Ann Hematol (1998) 76:73–80

ORIGINAL ARTICLE

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Meropenem monotherapy versus combination therapy with ceftazidime and amikacin for empirical treatment of febrile neutropenic patients

Received: 13 June 1997 / Accepted in revised form: 5 December 1997

Abstract Infections remain the major cause of morbidity and mortality among neutropenic cancer patients. The current study addresses the question whether monotherapy with the new broad-spectrum carbapenem meropenem exhibits efficacy comparable to that of the standard combination therapy with ceftazidime and amikacin for empirical treatment of febrile neutropenic patients. Seventy-one patients with hematological malignancies (55%) or solid tumors (45%), neutropenia $<500/\mu$l, and fever $>38.5\,^{\circ}$C were randomly assigned to either meropenem (1 g every 8 h) or ceftazidime (2 g every 8 h) and amikacin (15 mg/kg/day) intravenously. Meropenem ($n=34$) and ceftazidime/amikacin ($n=37$) were equivalent with respect to the clinical response at 72 h (62% versus 68%) ($p>0.05$) and at the end of unmodified therapy (59% versus 62%). Gram-positive bacteremia responded poorly in the meropenem and ceftazidime/amikacin group (29% versus 25%), whereas all gram-negative bacteremias responded except for one in the meropenem group caused by *Pseudomonas aeruginosa*. All patients survived to 72 h. One patient in each group died of gram-positive sepsis resistant to study medication. No significant side effects occurred in any regimen. This study suggests that meropenem monotherapy might be as effective as combination therapy with ceftazidime and amikacin for the empirical treatment of febrile neutropenic patients.

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Key words Leukemia · Neutropenia · Infection · Antibiotics · Meropenem

Introduction

Infections remain the major cause of morbidity and mortality among neutropenic cancer patients [5]. Depending on the severity and duration of neutropenia, documented infections and unexplained fever occur in 60–90% of neutropenic episodes [3]. These infections are responsible for 10–20% of the mortality seen in neutropenic cancer patients [3], due predominantly to sepsis [2] and pneumonia [27].

Because of the high rate of death due to infections in neutropenic cancer patients, the therapy is started at the first sign of infection and before the causative pathogen has been identified (empirical treatment). For two decades, combination therapy with an antipseudomonal β-lactam antibiotic and an aminoglycoside such as ceftazidime plus amikacin has been considered as the standard empirical treatment for fever in neutropenic cancer patients [14], and 60–70% of infections respond to this broad-spectrum combination therapy [4, 18, 25, 31]. However, more recently third-generation cephalosporins like ceftazidime [35] or carbapenems such as imipenem-cilastatin offer well-tolerated and cost-effective monotherapy with a clinical efficacy comparable to that of combination therapy [9, 10, 34]. Due to the increase in primary gram-positive infections, however, the response to monotherapy with ceftazidime has become unsatisfactory [10, 33]. Imipenem-cilastatin, on the other hand, has been hampered by adverse effects such as seizures, nausea, and vomiting [15, 34].

Meropenem is a new broad-spectrum carbapenem which is at least as active as ceftazidime in vitro against *Pseudomonas aeruginosa* [24] but also shows good activity against gram-positive bacteria [6, 39, 40]. It does not require the co-administration of an enzyme inhibitor, and no central nervous system toxicity or any other significant side effects have been reported in clinical

trials thus far [11, 20, 22]. These characteristics make meropenem a promising agent for empirical monotherapy and prompted us to assess the efficacy and tolerability of meropenem as empirical therapy for documented infections and unexplained fever in neutropenic cancer patients, in comparison to ceftazidime plus amikacin as the standard regimen.

Patients and methods

Study design

The present study was designed as an open prospective randomized trial of meropenem versus ceftazidime plus amikacin for the empirical treatment of clinically or microbiologically documented infections as well as unexplained fever in neutropenic cancer patients. The study was initiated after being approved by the ethical committees at the participating institutions and was conducted in accordance with the declaration of Helsinki. Every patient gave informed consent after having been informed about the investigational nature of the study.

Patient selection

For inclusion in the study, patients were required to meet all of the following criteria: (a) neutropenia (neutrophils $<500/\mu l$); (b) fever (rectal or oral temperature $\geq 38.5\,^{\circ}C$ or two temperatures $\geq 38.0\,^{\circ}C$ more than 30 min apart within a period of 12 h, not associated with drug administration or transfusion of blood products); (c) written informed consent.

Patients were excluded under the following conditions: (a) infections caused by pathogens with proven resistance to meropenem or ceftazidime and amikacin already known at study entry; (b) age <18 years; (c) pregnancy or lactation; (d) allergy to β-lactam antibiotics or aminoglycosides; (e) concurrent application of other investigational drugs; (f) cystic fibrosis; (g) previous entry to the trial during the same neutropenic episode; (h) history of seizures or CNS-localized leukemia; (i) hepatic failure or coma; (j) allogeneic bone marrow transplantation; (k) administration of any parenteral antibiotics in the 3 days prior to study medication.

Therapy

Upon the fulfillment of entry criteria patients were randomized in a 1:1 ratio between the two treatment arms using preformed randomization lists provided by the study center. Meropenem (Zeneca GmbH, 68723 Plankstadt, Germany) was administered at a dose of 1 g every 8 h by intravenous infusion for 20–30 min. Patients assigned to combination therapy received ceftazidime as a 2-g dose every 8 h by intravenous infusion. Amikacin was administered initially at 15 mg/kg per day in 2 or 3 equally divided doses parenterally; it was subsequently adjusted to serum levels. Unless signs of progressive unexplained fever or infection developed, both regimens were continued for at least 7 days. Dependening on early response at 72 h, additional antimicrobial agents were allowed to be added or therapy could be completely changed.

Investigations

Hematological and biochemical laboratory variables were determined prior to treatment, after 2–4 days of treatment, at least once weekly during treatment, and within 24 h after stopping therapy. Blood cultures were obtained prior to treatment and whenever there was a recurrence of fever. Chest X-rays or CT scans and invasive diagnostic procedures such as bronchoalveolar lavage were performed when indicated. Any adverse events occurring during the study were recorded. An organism was considered resistant to meropenem if the inhibitory zone diameter was ≤ 10 mm (using 10-μg discs), resistant to ceftazidime and amikacin if the inhibitory zone diameter was ≤ 14 mm.

Classification of infections

Infections were classified into the three subgroups with unexplained fever, clinically documented infection, and bacteremia according to PEG criteria [25]. Unexplained fever was defined as fever (rectal or oral temperature $\geq 38.5\,^{\circ}C$, not associated with drug administration or transfusion of blood products) and no clinical or microbiological evidence of infection. Clinically documented infection was defined as fever $\geq 38.5\,^{\circ}C$ and clinical evidence of infection with or without microbiological documentation. Bacteremia was defined as fever $\geq 38.5\,^{\circ}C$ and at least one positive blood culture. Only for coagulase-negative staphylococci and corynebacteria were two identical positive cultures from separate blood samples mandatory. Patients with bacteremia and clinical symptoms of infection were evaluated in the subgroup bacteremia.

Evaluation of response to therapy

The primary end point of the study was the clinical response of all episodes at 72 h after the onset of study medication. Clinical response was defined as defervescence $<37\,^{\circ}C$ and improvement of clinical signs of infection.

Secondary end points comprised the clinical response at the end of unmodified study medication and the relapse rate up to 14 days after termination of study therapy (follow-up period). These criteria were also applied to analysis of the subgroups with unexplained fever, clinically documented infection, and bacteremia. For bacteremia, bacteriological response was defined as bacteriologically proven eradication of the organism or presumed eradication because of clinical response. It was evaluated at the completion of unmodified study therapy. All patients were included in the assessment of the overall and infection-related mortality as well as of non-drug-related and drug-related adverse events. Mortality and adverse events were evaluated until 14 days after termination of study medication. If the patient was still neutropenic at this time, the evaluation was continued until recovery of neutrophils to $>500/\mu l$.

Statistical analysis

It was planned to enrol 78 patients in the study to detect a significant difference between the meropenem group and the ceftazidime/amikacin group with an 80% power ($\beta=0.2$) at a significance level of 5% ($\alpha<0.05$) in a two-tailed chi-square test, assuming a clinical response at 72 h of 80% in the group with ceftazidime plus amikacin and 50% in patients undergoing meropenem treatment. Thus, this pilot study was able to detect only major differences between the two arms.

Results

Patients

Seventy-one patients with 78 evaluable episodes were included in the study between January 1993 and October 1994 from the Departments of Hematology/Oncology of the University of Göttingen ($n=29$), Hannover

Table 1 Patient demography

	Meropenem ($n=34$)	Ceftazidime/amikacin ($n=37$)
Sex (male/female)	22/12	24/13
Age (years: median/range)	46/18–76	50/22–70
Underlying malignancy		
Hematological malignancy	17 (50%)	22 (59%)
– Acute myeloid leukemia	6	9
– Acute lymphocytic leukemia	2	2
– Chronic myeloid leukemia	1	1
– Non-Hodgkin's lymphoma	8	8
– Multiple myeloma	0	2
Solid tumor	17 (50%)	15 (41%)
Duration from onset of study therapy until neutrophil recovery >500/μl (days: median/range)	5/2–20	7/2–34
Oral antimicrobial prophylaxis	32 (94%)	35 (95%)

Medical School ($n=25$), University of Würzburg ($n=16$), and Evangelical Hospital Essen-Werden ($n=8$). Thirty-nine cases were randomized to each treatment arm. Seven patients (five in the meropenem and two in the ceftazidime/amikacin group) were excluded from the evaluation of clinical and bacteriological efficacy because of protocol violations, i.e., no neutropenia at study entry ($n=5$), additional intravenous antibiotics given during first study day ($n=1$), duration of study therapy <48 h ($n=1$). Thus, 64 patients with 71 episodes were evaluable for the clinical and bacteriological response (Tables 1–6), whereas all 71 patients with 78 episodes were assessed for overall and infection-related mortality (Table 7) and adverse events (Table 8).

Demographic patient characteristics (Table 1) such as sex, age, underlying malignancy, days from onset of study therapy until neutrophil recovery >500/μl, and oral antimicrobial prophylaxis were balanced between the two treatment groups ($p>0.05$, chi-square test).

Infection diagnosis

The meropenem and ceftazidime/amikacin group did not differ in the incidence of unexplained fever (56% versus 62%), bacteremia (32% versus 24%), or clinically documented infection (12% versus 14%) (Table 2). In the meropenem group, bacteremia was caused predominantly by gram-positive bacteria (64%), whereas gram-negative bacteria were the leading cause of bacteremia in the ceftazidime/amikacin group (56%).

Clinical response

The median duration of treatment with meropenem was 8 days (range, 3–17 days) in comparison to 6 days (range, 3–18 days) in the ceftazidime/amikacin group ($p>0.05$, chi-square test).

Table 2 Infection diagnosis

	Meropenem ($n=34$)	Ceftazidime/amikacin ($n=37$)
Unexplained fever (%)	19 (56)	23 (62)
Bacteremia (%)	11 (32)	9 (24)
Gram-positive	6/11	4/9
Gram-negative	4/11	5/9
Gram-positive + gram-negative	1/11	0/9
Clinically documented infection (%)	4 (12)	5 (14)

Table 3 Clinical response of all episodes

	Meropenem ($n=34$)	Ceftazidime/amikacin ($n=37$)
Response at 72 h		
Cured/improved	21 (62%)	25 (68%)
Unchanged/worse	13	12
Response at the end of study therapy		
Cured/improved	20	23
Cured with modification	4	3
Unchanged/worse	10	11
Relapse during follow-up	1	3

The two treatment groups did not differ in the clinical response at 72 h, at the end of study therapy, or in relapses during the follow-up period ($p>0.05$, chi-square test) (Table 3). In detail, 21 of 34 cases responded clinically to meropenem after therapy for 72 h (62%), whereas 25 of 37 cases were cured or improved in the ceftazidime/amikacin group (68%). At the end of study therapy, 20 of the 21 initial responders in the meropenem group and 23 of 25 cases in the ceftazidime/amikacin group were still improved without addition of

Table 4 Modification of the study therapy

	Meropenem ($n=9$)	Ceftazidime/amikacin ($n=6$)
Reason		
Persistent infection/unexplained fever	7	5
Resistent pathogen	2	1
Modification		
Glycopeptide	5	4
β-Lactam	1	1
Amphotericin B	2	0
Other agents	1	1

Table 5 Clinical response of episodes with unexplained fever, bacteremia, and clinically documented infection

	Meropenem	Ceftazidime/amikacin
Unexplained fever	($n=19$)	($n=23$)
Response at 72 h	16	17
Response at the end of study therapy		
Cured/improved	16	12
Cured with modification	0	5
Relapse during follow-up	1	2
Bacteremia	($n=11$)	($n=9$)
Response at 72 h	3	4
Response at the end of study therapy		
Cured/improved	2	4
Cured with modification	3	1
Relapse during follow-up	0	1
Clinically documented infection	($n=4$)	($n=5$)
Response at 72 h	2	4
Response at the end of study therapy		
Cured/improved	2	4
Cured with modification	1	0
Relapse during follow-up	0	0

Table 6 Bacteriological response of episodes with bacteremia at the end of unmodified study therapy

	Meropenem	Ceftazidime/amikacin
Total bacteriological response	5/11	6/9
Gram-positive	1/6	1/4
Streptococcus viridans	0/1	—
Streptococcus mitis	—	1/1
Strept. agalactiae, group B + Strept. faecalis	1/1	—
Streptococcus faecalis	—	0/1
Enterococcus sp., group D	—	0/1
Staphylococcus epidermidis	0/1	0/1
Staphylococcus sciuri + Staph. capitis	0/1	—
Staphylococcus sciuri	0/1	—
Staphylococcus aureus	0/1	—
Gram-negative	3/4	5/5
Pseudomonas aeruginosa	0/1	1/1
Escherichia coli	1/1	4/4
Enterobacter cloacae	1/1	—
Other gram-negative bacteria	1/1	—
Gram-positive + gram-negative	1/1	0/0
Corynebacterium sp., *E. coli*	1/1	—

Table 7 Mortality

	Meropenem ($n=39$)	Ceftazidime/amikacin ($n=39$)
Infection-related mortality	1	1
Causes of death	Bacteremia and septic shock (*Staphylococcus sciuri, Staphylococcus capitis*)	Bacteremia and septic shock (*Enterococcus* sp., group D)
Non-infection-related mortality	2	3
Causes of death	Lymphocytic lymphoma Lymphocytic lymphoma	Lung carcinoma Cardiac failure Lymphocytic lymphoma

Table 8 Adverse events

	Meropenem ($n=39$)	Ceftazidime/amikacin ($n=39$)
Drug-related	5 (13%)	6 (15%)
Diarrhea	2	1
Nausea	1	–
Rash	1	–
Alkaline phosphatase increase	1	–
SGOT increase	–	2
SGPT increase	–	2
Bilirubin increase	–	1
Non-drug-related		
Diarrhea	3	6
Nausea	–	3
Vomiting	1	3
Rash	–	2
Paresthesia	–	1
Herpes simplex infection	1	2
Apnea	–	1
Shock	1	2
Esophageal tear	1	–
Toothache	–	1
Liver rupture	–	1
Sepsis	–	1
Alkaline phosphatase increase	–	1
Bilirubin increase	1	1

other antimicrobial agents, whereas four cases in the meropenem group and three in the ceftazidime/amikacin group improved only after modification of the initial study therapy (Table 3). The median time to defervescence was 4 days in both treatment groups.

Persistent infection or unexplained fever was the main reason for the modification of the initial regimen, and most often glycopeptides were added (Table 4). Two patients in the meropenem group were administered amphotericin B due to suspected fungal pneumonia, whereas no patient in the ceftazidime/amikacin group received amphotericin B as modification (Table 4).

Overall, 29% of the meropenem group and 30% of the ceftazidime/amikacin group were still nonresponders after the end of study therapy, with or without modification. During the follow-up period one additional patient relapsed in the meropenem group versus three patients in the ceftazidime/amikacin group (Table 3). At the end of unmodified therapy meropenem was more effective in fever of unknown origin (84% versus 52%) but less effective in bacteremia (18% versus 44%) and clinically documented infection (50% versus 80%) (Table 5).

Bacteriological response

For bacteremia, the bacteriological response at the end of unmodified study therapy was comparable for the two groups (Table 6). All gram-negative bacteremias responded to unmodified study therapy, except for one *Pseudomonas aeruginosa* bacteremia in the meropenem group. Overall, three of four gram-negative bacteremias and the one bacteremia caused by both gram-positive and gram-negative bacteria responded in the meropenem group (80%), whereas all five gram-negative bacteremias responded in the ceftazidime/amikacin group (100%). The bacteriological response rate for gram-positive bacteremia was poor in both groups. At the end of unmodified therapy, one of six gram-positive bacteremias and the one bacteremia caused by both gram-positive and gram-negative bacteria responded in the meropenem group (29%), whereas one of four gram-positive bacteremias responded in the ceftazidime/amikacin group (25%).

Mortality

There were no deaths during the first 72 h of therapy. Two patients died during neutropenia, one in each treatment group. Both nonsurvivors suffered from acute myeloid leukemia and died after the completion of study therapy of septic shock due to gram-positive bacteria (Table 7). The nonsurvivor in the meropenem group suffered from septic shock with *Staphylococcus sciuri* and *Staphylococcus capitis* resistant to meropenem and died on study day 14, while the nonsurvivor in the ceftazidime/amikacin group died on study day 12 of septic shock with *Enterococcus* sp., group D, resistant against ceftazidime and amikacin. After recovery from neutropenia two patients in the meropenem group and

three in the ceftazidime/amikacin group died of non-infection-related causes, predominantly progression of underlying malignant disease. No deaths were related to the study medication.

Adverse events

Analysis of side effects was related to all 78 reported episodes (Table 8). Adverse events were reported during five of the 39 courses of meropenem therapy (13%) and during six of the 39 courses of ceftazidime/amikacin (15%). All side effects were mild to moderate and consisted predominantly in a slight increase in liver enzymes and/or bilirubin. In addition, episodes of skin rash, diarrhea, and nausea were encountered. All side effects resolved completely after the termination of antimicrobial and antineoplastic therapy.

Discussion

Up to now, the combination of a β-lactam antibiotic and an aminoglycoside such as ceftazidime plus amikacin has been regarded as the standard empirical therapy for infectious complications in neutropenic patients with malignant disorders [4, 14, 25, 31]. The improved efficacy and broad antimicrobial spectrum of new β-lactam antibiotics such as third-generation cephalosporins (e.g., ceftazidime) and carbapenems (e.g., imipenem-cilastatin or meropenem) offer a promising alternative. These agents are easy to administer, cost less than combination therapy [41], do not require monitoring of serum levels, and lack the potential ototoxicity and nephrotoxicity associated with aminoglycosides.

Meropenem is a new broad-spectrum carbapenem which provides a very similar spectrum of antibacterial activity to that of imipenem, with potent activity against a variety of gram-positive aerobes, gram-negative aerobes, and anaerobic species [6, 39, 40]. In vitro it is slightly less active than imipenem against gram-positive bacteria but exerts a higher activity against gram-negative organisms, including some imipenem-resistant strains of *Pseudomonas aeruginosa*, [12, 19, 38], by virtue of more rapid drug entry [36]. Meropenem is at least as active as ceftazidime in vitro against *Pseudomonas aeruginosa* [24]. Unlike imipenem, meropenem is not significantly degraded by renal tubular dehydropeptidase-1 and therefore does not require the co-administration of an inhibitor, such as cilastatin. Its pharmacology is otherwise very similar to that of imipenem [1, 23]. The toxicity profile of meropenem is comparable to that of imipenem except that data from animal studies suggest that meropenem may be less epileptogenic and less nephrotoxic. Meropenem has been shown to be effective in several animal models [13]. In clinical trials, it has been used successfully to treat pneumonia [26, 29], meningitis [11, 21, 37], intra-abdominal infections [16, 17, 20], soft tissue infections [22, 30], bacteremia [29], and urinary tract infections [8, 29].

More recently, the Meropenem Study Group of Leuven, London, and Nijmegen reported the first randomized trial of meropenem in neutropenic patients. They evaluated the efficacy of meropenem versus ceftazidime as monotherapy for fever in neutropenic patients with hematological malignancies and solid tumors [28]. Of the 151 evaluable episodes treated with ceftazidime and the 153 treated with meropenem, 62 (41%) and 67 (44%), respectively, responded to the initial regimens without modifications. In this study meropenem was clinically as effective as ceftazidime and well tolerated, with no evidence of nausea or central nervous system toxicity.

However, there are data from a large randomized clinical trial of the EORTC study group, which has studied ceftazidime combined with short or long courses of amikacin, suggesting that combination therapy is still of critical importance, at least for the most serious infections such as gram-negative bacteremias [14].

For this reason, the present multicenter trial assessed the efficacy of meropenem versus the standard combination therapy with ceftazidime plus amikacin as empirical treatment for documented infections and unexplained fever in neutropenic cancer patients. Although half of the patients suffered from solid tumors, the study population was severely neutropenic with a median duration of 6 days (range, 2–34) from the onset of study therapy until neutrophil recovery to $>500/\mu l$. Under these conditions, meropenem and ceftazidime/amikacin did not differ in the clinical response at 72 h (62% versus 68%) or at the end of unmodified study therapy (59% versus 62%).

Without effective antimicrobial treatment, gram-negative bacteria are responsible for a high early death rate during neutropenia and are therefore the primary target of empirical therapy. Most importantly, in the present trial no patient died of gram-negative sepsis. This demonstrates the potency of both meropenem monotherapy and combination therapy with ceftazidime and amikacin against gram-negative bacteria. All gram-negative bacteremias even responded to study medication without addition of further antimicrobial agents, except for one in the meropenem group caused by *Pseudomonas aeruginosa*.

However, bacteremia caused by gram-positive pathogens responded very poorly in the meropenem group as well as in the group with ceftazidime and amikacin (29% versus 25%). Therefore, the improved gram-positive activity of meropenem against streptococci and staphylococci in vitro did not translate to an improved bacteriological and clinical response in vivo. Consistent with current trends, 50% of all bacteremias in the present trial were caused by gram-positive bacteria, which were also responsible for the two deaths during neutropenia. After the completion of study medication one patient in each group died of septic shock caused by gram-positive bacteria resistant to study medication, *Staphylococcus sciuri* plus *Staphylococcus*

capitis in the meropenem group and *Enterococcus* sp., group D, in the group with ceftazidime plus amikacin. However, these deaths occurred on study days 12 and 14 and are not the main target of the empirical therapy, which should primarily prevent early death during the first 3 days of therapy. On the other hand, the poor clinical and bacteriological efficacy of meropenem with regard to gram-positive bacteremia in the current trial suggests that there is no reason to delay the addition of glycopeptides to meropenem when there is no clinical response after 72 h of treatment.

It is very encouraging that meropenem monotherapy was more effective than combination therapy with ceftazidime and amikacin in patients with fever of unknown origin (84% versus 52%). On the other hand, meropenem was less effective in patients with bacteremia (18% versus 44%) and clinically documented infection (50% versus 80%). The lower clinical efficacy of meropenem in bacteremia was probably caused by the higher incidence of gram-positive bacteremias, which responded poorly in both groups, whereas two suspected fungal pneumonias with the requirement of amphotericin B treatment explain the lower efficacy in clinically documented infections. However, no definite conclusions can be drawn from these subgroup analyses because of the small number of patients.

During meropenem therapy, adverse events of mild to moderate degree were encountered, but their spectrum was not comparable to common side effects of imipenem. Only one patient developed mild nausea, and no vomiting, seizures, or any other relevant toxicity was documented.

The assessment of outcome depends critically on how the primary end point of the study is defined. The present trial has chosen as the primary end point the clinical response at the end of the true empirical treatment period of 72 h. In fact, there were no deaths during the first 72 h, and both regimens showed equal clinical efficacy (62% versus 68%). Moreover, meropenem and ceftazidime plus amikacin were also equivalent in primary end points chosen by other groups, such as response at the end of unmodified therapy (59% versus 62%) used by the Meropenem Study Group of Leuven, London, and Nijmegen [28] or mortality during neutropenia proposed by Pizzo and co-workers [32].

Simultaneous with the present trial, a collaborative study between EORTC-IATCG and the GIMEMA Infection Program compared monotherapy with meropenem and combination therapy with ceftazidime and amikacin as empirical therapy for fever in granulocytopenic patients with cancer [7]. A successful outcome without any change in the allocated regimen was reported in 270 of 483 (56%) patients treated with monotherapy compared with 245 of 475 (52%) patients treated with the combination regiment [7]. Although the present study is much smaller, the results are in accordance with those of the study by the EORTC-IATCG/GIMEMA Infection Program; they suggest that meropenem monotherapy might provide an effective and well-tolerated alternative to conventional combination regimens such as ceftazidime plus amikacin for the empirical therapy of infections and unexplained fever in neutropenic patients with hematological malignancies or solid tumors.

Acknowledgements The authors thank Dr. E. Schachner-Wünschmann, Dr. K. Faulkner, Dr. A. Dumke, and Dr. G. Beck from Zeneca GmbH for their assistance in organization and clinical monitoring.

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