ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1996, p. 1108–1115 Vol. 40, No. 5
0066-4804/96/$04.00+0

Monotherapy with Meropenem versus Combination Therapy with Ceftazidime plus Amikacin as Empiric Therapy for Fever in Granulocytopenic Patients with Cancer

A. COMETTA,[1]* T. CALANDRA,[2] H. GAYA,[3] S. H. ZINNER,[4] R. DE BOCK,[5] A. DEL FAVERO,[6] G. BUCANEVE,[6] F. CROKAERT,[7] W. V. KERN,[8] J. KLASTERSKY,[7] J. LANGENAEKEN,[7] A. MICOZZI,[9] A. PADMOS,[10] M. PAESMANS,[7] C. VISCOLI,[11] M. P. GLAUSER,[1] AND THE INTERNATIONAL ANTIMICROBIAL THERAPY COOPERATIVE GROUP OF THE EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER AND THE GRUPPO ITALIANO MALATTIE EMATOLOGICHE MALIGNE DELL'ADULTO INFECTION PROGRAM†

Division of Infectious Diseases, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland[1]; The Picower Institute for Medical Research, Manhasset, New York[2]; Department of Microbiology, Brompton Hospital, London, United Kingdom[3]; Division of Infectious Diseases, Department of Medicine, Brown University, Rhode Island Hospital and Roger Williams Medical Center, Providence, Rhode Island[4]; Department of Hematology, Middelheim Ziekenhuis, Antwerp,[5] and Department of Medicine, Institut Jules Bordet, Brussels,[7] Belgium; Istituto Medicina Interna e Scienze Oncologiche, Policlinico Monteluce, Perugia,[6] and Department of Hematology, Universita "La Sapienza," Rome,[9] and Clinical Immunology Service-Infectious Diseases of the Compromised Host, University of Genova and National Institute for Cancer Research, Genoa,[11] Italy; Sektion Infektiologie und Klinische Immunologie, Medizinische Universitätsklinik und Poliklinik, Ulm, Germany[8]; and Kingston Regional Cancer Centre and the Department of Oncology, Queen's University, Kingston, Ontario, Canada[10]

Received 10 November 1995/Returned for modification 5 January 1996/Accepted 27 February 1996

Combinations of beta-lactams plus aminoglycosides have been standard therapy for suspected infections in granulocytopenic cancer patients, especially those with profound long-lasting granulocytopenia. With the advent of new broad-spectrum bactericidal antibiotics such as extended-spectrum cephalosporins or carbapenems, the need to combine beta-lactams with aminoglycosides became more controversial. The objective of this prospective randomized multicenter study was to compare the efficacy, safety, and tolerance of meropenem monotherapy with those of the combination of ceftazidime plus amikacin for the empirical treatment of fever in granulocytopenic cancer patients. Of 1,034 randomized patients, 958 were assessable in the intent-to-treat analysis for response to antibacterial therapy, including 483 in the meropenem group and 475 in the ceftazidime-plus-amikacin group. The median durations of neutropenia were 16 and 17 days, respectively. A successful outcome was reported in 270 of 483 (56%) patients treated with monotherapy compared with 245 of 475 (52%) patients treated with the combination group ($P = 0.20$). The success rates in the monotherapy group and the combination group were similar by type of infection (single gram-negative bacteremia, single gram-positive bacteremia, clinically documented infection, and possible infection). The occurrence of further infections assessed in patients for whom the allocated regimen was not modified did not differ between the two groups (12% in both groups). Mortality due to the presenting infection or further infection was relatively low (8 patients treated with the monotherapy compared with 13 patients treated with the combination). A total of 1,027 patients were evaluable for adverse events; the proportion of those who developed adverse effects was similar between the two groups (29% in both groups), and only 19 (4%) patients in the monotherapy group and 31 (6%) in the combination group experienced an adverse event related or probably related to the study drug. Allergic reactions were the only reason for stopping the protocol antibiotic(s) (3 and 5 patients, respectively). This study confirms that monotherapy with meropenem is as effective as the combination of ceftazidime plus amikacin for the empiric treatment of fever in persistently granulocytopenic cancer patients, and both regimens were well tolerated.

Cancer patients who become granulocytopenic as a result of intensive myelosuppressive chemotherapy are at high risk of developing infections (31, 36) which may be lethal if empiric antibiotic treatment is not instituted at the first sign of infection (36). For the past 2 decades, combinations of beta-lactams

* Corresponding author. Mailing address: Division of Infectious Diseases. Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland. Phone: 41 21 314-10.09. Fax: 41 21 314-02.98.

† The following were included in the Program. Participants (no. of patients): P. Martino, Rome, Italy (86); D. Caballero, Salamanca, Spain (58); W. V. Kern, Ulm, Germany (54); D. Engelhard and M. Shapiro, Jerusalem, Israel (50); E. Castagnola, L. Massimo, and R. Giacchino, Genoa, Italy (50); M. Sanz, Valencia, Spain (42); M. Giacchino, Turin, Italy (36); M. Aoun, Brussels, Belgium (34); B. Oppenheim, Manchester, England (34); D. D'Antonio, Pescara, Italy (33); F. Follath, Zurich, Switzerland (30); G. Barbabietola and F. Menichetti, Perugia, Italy (31); M. Montillo, Ancona, Italy (30); M. T. Van Lint, Genoa, Italy (28); A. Cometta, Lausanne, Switzerland (28); B. Gibson, Glasgow, Scotland (26); L. Resegotti, Turin, Italy (25); C. Kibbler and H. Prentice, London, England (25); A. van Hoof and H. van Landuyt, Bruges, Belgium (21); P. Ricci and G. Rosti, Bologna, Italy (20); A. Efremidis, Athens, Greece (17); F. Di Raimondo, Catania, Italy (17); R. Hemmer, Luxembourg, Luxembourg (14); M. Hatjiyanni and B. Seitanides, Pireaus, Greece (14); D. Amsallen and J. M. Estavoyer, Besançon, France (13); G. Petrikkos, Athens, Greece (13); A. Porcellini, Cremona, Italy (13); Z. Berneman, Edegem, Bel-

and aminoglycosides have been standard therapy for suspected infections in granulocytopenic patients, especially in those with profound long-lasting granulocytopenia (4). The rationale for the use of aminoglycoside-containing combinations was the prospect of synergistic bacterial killing (11), which has been reported to improve outcome in profoundly neutropenic cancer patients with gram-negative bacteremia (7). In addition, the usefulness of aminoglycosides in neutropenic patients with gram-negative bacteremia had been emphasized in a previous study from our group that reported a better outcome with a full course of amikacin plus ceftazidime than with a short course (3 days) of the aminoglycoside and a full course of ceftazidime (12).

The advent of new broad-spectrum bactericidal antibiotics, such as extended-spectrum cephalosporins or carbapenems, has offered the prospect of single-agent therapy (27, 32, 34, 38). Although some prior studies suggest that monotherapy is as effective as beta-lactam-plus-aminoglycoside combinations, the limited number of randomized patients and consequent limited statistical power, the relatively small proportion of patients with long-standing granulocytopenia, and the small number of patients with gram-negative bacteremia do not allow definitive conclusions about the role of single-agent therapy. One recent publication (8) showed that in 876 febrile neutropenic episodes, ceftazidime alone was as effective as a combination of piperacillin plus tobramycin. However, the use of piperacillin as the beta-lactam agent in the combination arm might not have been the most appropriate comparator in view of the dissemination of beta-lactamase-producing organisms (12, 14). Indeed, resistance was a more frequent reason for failure in the combination group than in the monotherapy group; in addition, the bacterial eradication rate in gram-negative bacteremias was lower in the piperacillin-tobramycin group than in the ceftazidime group.

Moreover, over the last 10 years there has been a continuous shift in the type of microorganisms recovered from the blood of granulocytopenic cancer patients with a considerable reduction of gram-negative bacteremic episodes, including those due to *Pseudomonas aeruginosa*, and a significant increase in gram-positive isolates (6, 30). Thus, the need for the aminoglycoside-containing combination must be reassessed in view of this striking epidemiological change.

With their excellent microbiological activity against both gram-negative (including *P. aeruginosa*) and gram-positive bacteria, with the exception of enterococci and methicillin-resistant staphylococci (10), carbapenems represent very good alternatives to extended-spectrum cephalosporins as empirical treatment of fever in granulocytopenic cancer patients. Imipenem/cilastatin, the first available carbapenem, has been used in several studies (27, 28, 34, 39); however, the administration of high doses (50 mg/kg of body weight per day, i.e., 3 to 4 g/day in adults) has been complicated by considerable gastrointestinal toxicity (17). Monotherapy with meropenem, a new carbapenem with a broad-spectrum of activity similar to that of imipenem/cilastatin, has been shown to be as effective as ceftazidime for the empirical treatment of febrile neutropenic patients in a recently published study (37); in addition, meropenem was very well-tolerated, since no digestive toxicity was reported.

The present study was a prospective, randomized, multicenter trial to test the concept of monotherapy versus combination therapy for the empirical treatment of fever in cancer patients with profound and prolonged granulocytopenia. The objectives of the present trial were to evaluate and compare the safety, tolerance, and efficacy of meropenem alone with those of ceftazidime plus amikacin.

(This work was presented in part at the International Congress of Chemotherapy, Montreal, Canada, 17 to 20 July 1995.)

MATERIALS AND METHODS

This protocol was designed in accordance with the guidelines published by the Immunocompromised Host Society (19).

Patient eligibility. In this trial, the International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC) consisted of 28 centers located in Europe and in the Middle East and of 13 Italian centers of the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Infection Program. Eligible patients older than 3 months included those with cancer and those who had undergone bone marrow transplantation for neoplastic disease. Patients were eligible for randomization if they had fever ($\geq$38.5°C on one occasion or $\geq$38°C on two or more occasions within 12 h), granulocytopenia (absolute granulocyte count of $\leq$1,000 cells per μl, anticipated to decrease to fewer than 500 cells per μl within 24 to 48 h), and a presumed infection (i.e., fever not likely to be due to a noninfectious cause such as drug or blood product administration, etc.). All patients or parents of children were informed about the investigative nature of this study and provided informed consent. The trial was conducted in accordance with the Declaration of Helsinki and all applicable national and local ethical requirements. The protocol was also approved by the EORTC Protocol Review Committee (EORTC study number 46931) and by the Ethics Committee of each participating institution.

Patients were excluded from the trial if they had received any intravenous antibiotic during the granulocytopenic episode or during the preceding 96 h, had a known allergy to any of the protocol antibiotics, had been previously randomized in this protocol or received treatment with any investigational drug within the 30 days preceding randomization, had renal failure requiring hemo- or peritoneal dialysis or a serum creatinine level of greater than 300 μmol/liter or 3.5 mg/dl or an estimated creatinine clearance of less than 25 ml/min for adults (renal impairment in children who were less than 14 years old was defined as a serum creatinine level higher than the upper limit of the normal pediatric range), were less than 3 months of age, were pregnant, or had known human immunodeficiency virus infection.

Randomization procedure. Patients were randomized centrally by connection with the IATCG randomization computer located in the IATCG Data Center at the Institut Bordet in Brussels, Belgium. The program was accessible 24 h a day, 7 days a week, with a touch-tone phone, through a vocal interface card installed in the computer. Investigators directly entered the data into the computer after verification of patient eligibility and then received treatment allocation. The randomization algorithm used the minimization technique of the imbalances between the two treatment arms with two stratification variables, the underlying disease (stratum 1, leukemia and bone marrow transplantation [for any reason]; stratum 2, lymphoma and solid tumors) and the center (16, 33). A supply of emergency envelopes was kept at each center to be used only in the event of computer failure or a problem with phone communication. Data relative to patients randomized by envelopes were entered into the data base manually for the calculation of imbalances and, therefore, were considered for subsequent randomizations. Patients were randomized only once into the study.

Hypothesis and sample size calculation. The primary objective of the trial was to compare the success rates of both regimens. According to three previous studies (12, 13, 20), the expected overall response to ceftazidime plus amikacin was 75% among all evaluable patients. To detect an absolute increase of 10% for the overall response rate in the meropenem arm, with a two-sided test with a type I error level of 5% and a power in excess of 90%, 413 evaluable patients had to be included in each treatment arm. Under the assumption from previous IATCG-EORTC trials (12, 13, 20) that 80% of the eligible patients would be evaluable for response to therapy, a total of 1,032 eligible patients had to be entered into the study.

gium (12); M. Carotenuto, San Giovanni Rotondo, Italy (12); R. de Bock, Antwerp, Belgium (11); A. Lopez, Barcelona, Spain (11); J. M. Andrien and R. Paulus, Verviers, Belgium (9); B. Martino and F. Nobile, Reggio di Calabria, Italy (9); P. Togni, Bellinzona, Switzerland (9); A. Ferster, Brussels, Belgium (9); L. Cudillo, Rome, Italy (8); J.-C. Legrand, Charleroi, Belgium (7); A. Dinota, Potenza, Italy (6); A. Cajozzo and G. Quintini, Palermo, Italy (5); A. Martinez-Dalmau, Vigo, Spain (5); and A. Nosari, Milan, Italy (3). Data Review Committee: R. de Bock, G. P. Bucaneve, A. Cometta, F. Crokaert, H. Gaya, W. V. Kern, J. Langenaeken, A. Micozzi, A. Padmos, and M. Paesmans. Data Manager: J. Langenaeken. Statistician: M. Paesmans. Microbiology Reference Center: M. Galazzo, M. Giddey, and J. Bille, Clinical Microbiology Laboratory, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland. Consultant for aminoglycoside monitoring: J. Blaser, Department of Internal Medicine, Universitätsspital, Zürich, Switzerland.

A secondary objective was a comparison of the success rates of both regimens among patients with single gram-positive bacteremia. With the inclusion of 1,032 eligible patients, we estimated that 87 episodes of gram-positive bacteremia would occur in each treatment group, which would be sufficient to demonstrate an increase of the response rate from 40% with ceftazidime plus amikacin to 65% with meropenem, using a two-sided test with a type I error level of 5% and a power of 90%.

Interim analyses for efficacy and occurrence of serious unwanted events were planned and performed after the inclusion of 200 and 500 patients in the trial with delineated predetermined stopping rules in case of an unacceptable difference in efficacy and toxicity between the regimens. Comparison tests were performed by using a significance cutoff at a P value of 0.02 in order to maintain a final significance level near 5% after two interim analyses.

Clinical and laboratory evaluation. Complete histories were taken and physical examinations, routine chest X rays as well as a complete battery of laboratory tests, including urine culture and two sets of blood cultures (from different venipunctures at 30-min intervals), were performed for all patients prior to initiating study antibiotics. Other cultures were performed as clinically indicated.

Follow-up studies included repeat hematological analyses, coagulation studies, chemistry, and urinalyses as prescribed by the protocol. Blood cultures were repeatedly taken daily for persistent fever or bacteremia analysis until the cultures gave negative results.

Bacteria isolated from blood were sent to the Microbiological Reference Center (Clinical Microbiology Laboratory, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland), where standardized bacterial identification and antibiotic susceptibility tests were performed (1, 21, 35). Antimicrobial susceptibility was evaluated by using zone diameter interpretive standards and equivalent MICs recommended by the National Committee for Clinical Laboratory Standards; breakpoints for resistance included inhibitory zone diameters of 10 mm or less for meropenem and 14 mm or less for ceftazidime and amikacin or MICs of 16 μg/ml or more for meropenem and 32 μg/ml or more for ceftazidime and amikacin.

Classification of febrile episodes and evaluation of response. Primary febrile episodes were classified (19) as (i) microbiologically documented infections with or without bacteremia, (ii) clinically documented infections, (iii) unexplained fever, or (iv) noninfectious fever (such as neoplastic fever, chemotherapy-induced fever, graft versus host diseases, and transfusion-induced fever). Patients were evaluated between 72 and 96 h after the initiation of empiric therapy (i.e., early evaluation) and at the completion of the therapeutic trial (i.e., overall evaluation).

A patient's trial was evaluated as a success if fever and clinical signs of infection (whenever present) resolved and if the infecting microorganisms (whenever isolated) were eradicated without change of the allocated antibacterial therapy. The return to a normal temperature (i.e., less than 38°C) had to be maintained for at least 4 consecutive days to qualify as a treatment success. The primary infection must not have recurred within 1 week after discontinuation of protocol therapy.

A patient's trial was evaluated as a failure if (i) the patient died of the primary infection, (ii) bacteremia persisted beyond the first 24 h of therapy, (iii) breakthrough bacteremia was documented, (iv) the documented pathogen was resistant to the allocated beta-lactam regardless of the evolution of the patient's clinical condition, or (v) no response was seen after at least 72 h of empiric therapy, which usually prompted modification of or addition to the protocol antibacterial therapy in an attempt to eradicate the primary infection. However, premature modification (occurring before 72 h) of the allocated regimen was allowed and the result was considered a failure under one or more of the following conditions: development of shock, acute respiratory distress syndrome, disseminated intravascular coagulation or multiple organ failure; progression of the primary clinically documented infection and persistence of fever 48 h or more after the initiation of empirical therapy; microbiological documentation of the primary infection as a viral, fungal, or mixed (bacterial plus viral or fungal) infection. Persistence of fever was considered a cause for failure only after 72 h of the allocated regimen. If fever prompted a modification of treatment before 72 h, the cause for failure was described as treatment changed without adequate reason. For all gram-positive infections susceptible to the allocated beta-lactam, the persistence of fever in an otherwise stable patient was not considered a sufficient criterion for the modification of protocol therapy; if treatment was changed under such circumstances, the patient trial was considered a protocol violation in the analysis of efficacy (but a failure in the intent to treat analysis).

A patient's trial was classified as nonevaluable for response to protocol antibacterial therapy if protocol violation precluded evaluation of the patient's response by the Data Review Committee.

Therapeutic regimens. Patients received either intravenous meropenem (1 g every 8 h [q8h] for adults and children weighing more than 50 kg, 20 mg/kg q8h for children weighing less than 50 kg) infused over a period of 20 to 30 min or ceftazidime (2 g q8h for adults, 35 mg/kg q8h for children) plus amikacin at 20 mg/kg/day given in a single daily dose. On the basis of the results of a previous trial which showed that the single daily dose of amikacin was as effective as and no more toxic than multiple daily doses (20), amikacin was administered as a single daily dose. Ceftazidime was administered first over 15 to 30 min and then amikacin was infused for a period of 30 min. It was recommended to monitor the levels of amikacin in serum twice weekly and to sample blood 8 h postinjection. Commercially available assays are designed to provide reliable data within the range of peak and trough levels encountered in most patients during multiple daily dosing; the concept of measuring the 8-h level in patients given a single daily dose allows determination of serum levels within the range of the best reproducibility and accuracy of commercial assays (2). Doses were adjusted to achieve an 8-h level in serum of ≤20 mg/liter. Monitoring of the levels of the beta-lactam antibiotics in serum was not required.

Duration of protocol therapy. Successful response to therapy in patients with microbiologically or clinically documented infections and in those with possible infections required that they received antibiotics for a minimum of 7 days, 4 of which were consecutive without fever. Investigators were allowed to discontinue antibiotics at day 4 for patients classified as having fever not related to infection.

Toxicity. Nephrotoxicity was defined as an increase in serum creatinine levels of 50% or greater than baseline values or a rise in serum creatinine levels (adults only) of greater than 45 μmol/liter. Ototoxicity was tested by an audiogram for patients with impaired hearing and was defined as a decline in inner ear function, either auditory (a 20-dB or greater decrease of auditory activity at any frequency in one or both ears) or vestibular (nystagmus, vertigo with nausea and vomiting, gait disturbances, or instability), without discernible physical causes. Hepatotoxicity was defined as an increase of transaminases or bilirubin or alkaline phosphatase 1.5 times above baseline values and normal ranges. Hypokalemia was defined as a decrease of 1.0 mmol/liter or more (without concomitant supply of potassium) or 0.5 mmol/liter or more (with concomitant supply of potassium) in the levels of potassium in serum from baseline values.

Adverse effects were recorded in the case report form and were judged to be definitely or probably related to the study drugs or definitely not or probably not related to the study drug(s).

Further infections and death. Further infections (i.e., secondary infections) were defined as those caused by a new organism not recognized as the initial pathogen and which occurred either during therapy with the allocated regimen or within a week after discontinuation of protocol antibiotics. Further infections were classified as microbiologically documented infections with or without bacteremia, clinically documented infections, or unexplained fever.

Death was attributed to infection when it occurred as a direct consequence of either the presenting infection or a further infection.

Analysis. All case report forms were reviewed by the Data Review Committee for completeness, accuracy, eligibility criteria, and assessment of the outcome variables. The committee was blinded to the assigned regimen. All data were entered into a computerized data base and analyzed by using SPSS programs or BMDP procedures (9, 29).

Two different analyses were conducted; an intent-to-treat analysis was performed for all eligible and evaluable patients, and a second analysis was done after exclusion of patients with fever not related to infection (assessed as success in the intent-to-treat analysis) and patients with treatment changed without adequate reason (assessed as failure in the intent-to-treat analysis).

Inferential analyses included contingency analyses by hypothesis tests based on asymptotic chi-square distributions (with a continuity correction in the case of dichotomous variables) or by Fisher's exact tests for small samples when necessary. Mann-Whitney tests were used for the comparison of continuous variables. Distributions of time-to-event variables were estimated by the nonparametric method described by Kaplan-Meier and were compared by the log rank test. Inferential multivariable analysis included use of the logistic regression model to estimate the probability distribution of a dichotomous variable (with a stepwise forward method for the selection of covariates). The covariates tested were all assessable at the time of randomization, and each of them was treated as a categorical variable represented by I-1 indicator variables, where I referred to its number of levels. All significance probabilities were calculated for two-tailed tests. For a better assessment of clinical significance, confidence intervals were also constructed (3).

RESULTS

From May 1993 to June 1994, 1,034 febrile granulocytopenic cancer adult and pediatric patients were randomized in the study, of whom 47 (22 patients in the meropenem group and 25 patients in the ceftazidime-plus-amikacin group) were not eligible for the following reasons: no neutropenia (8 and 4 patients), second randomization (3 and 8 patients), intravenous administration of an antibiotic within the 96 h preceding the randomization (5 and 2 patients), no fever (1 and 4 patients), no cancer (2 patients in each arm), documented infection at randomization (1 and 2 patients), and miscellaneous causes (2 and 3 patients). In addition, 29 eligible patients, 13 in the meropenem group and 16 in the ceftazidime-plus-amikacin group, were not assessable for efficacy for the following reasons: clinical course precluding evaluation (5 and 3 patients), error in allocation of treatment regimen (3 and 4 patients), antibiotic prophylaxis not discontinued (3 and 4 patients), early

TABLE 1. Characteristics of the 958 patients evaluable for response to therapy

Characteristic or parameter	Value	
	Meropenem	Ceftazidime + amikacin
Patients (*n*)	483	475
Adults	385 (80%)	385 (81%)
Children (1–16 yrs)	98 (20%)	90 (19%)
Age (median)	38 (1–81)	39 (1–77)
Sex (male/female)	275/208	266/209
Wt (kg) (median)	64 (9.3–120)	63 (6.1–114)
Underlying cancer		
Acute leukemia	278 (58%)	289 (61%)
Hodgkin's disease and lymphoma	90 (19%)	83 (17%)
Solid tumor	80 (16%)	71 (15%)
Other	35 (7%)	32 (7%)
Days of granulocytopenia ($\leq$1,000/mm^3)		
At study entry	5 (0–194)	5 (0–135)
Total	16 (1–79)	17 (2–78)
Granulocyte count		
Median at entry (cells per mm^3)	33 (0–986)	30 (0–1,000)
Patients with $<$100 cells per mm^3 at entry	321 (66%)	325 (68%)
Trial days with granulocytes at		
$\leq$100/mm^3	1,947 (57%)	1,967 (59%)
100–500/mm^3	719 (21%)	702 (21%)
501–1,000/mm^3	270 (8%)	232 (7%)
$>$1,000/mm^3	458 (14%)	420 (13%)
Oral antibacterial prophylaxis	352 (73%)[a]	347 (73%)[a]
Quinolones	281	277
Cotrimoxazole	62	57
Penicillin	25	26
Other	27	26
Oral antifungal prophylaxis	319 (66%)	321 (68%)
Oral antiviral prophylaxis	132 (27%)	113 (24%)
Intravenous catheter in situ	397 (82%)	386 (81%)
Catheter removed after randomization	102 (21%)	99 (21%)
Presence of shock at onset	11	5

[a] Totals of 42 and 39 patients, respectively, were given more than one antibiotic.

TABLE 2. Outcome of therapy (intent-to-treat analysis)

Outcome or modification	Value	
	Meropenem	Ceftazidime + amikacin
Duration of therapy (days)	7 (1–22)	7 (1–28)
Success	270 (56%)	245 (52%)
Failure	213 (44%)	230 (48%)
Reasons for modification of empiric antibiotic treatment		
Persistent fever	74	93
Resistant pathogen	41[a]	44[a]
Progression of primary infection	20	21
Treatment changed without adequate reason	19	21
Relapsing fever	17	11
Shaking chills and spiking fever	13	9
Breakthrough bacteremia	11	7
Persistence of bacteremia	5	6
Death from the primary infection	3	5
Withdrawal due to toxicity	3	5
Viral or fungal infection	4	3
Development of shock	2	4
Relapse of the primary infection	1	1[a]

[a] Totals of 44 pathogens isolated from 41 patients given meropenem and 46 pathogens isolated from 44 patients given ceftazidime plus amikacin were resistant to the allocated beta-lactam as follows (values are for the meropenem and ceftazidime-plus-amikacin groups, respectively): methicillin-resistant coagulase-negative staphylococci (34 and 33), *Enterococcus* spp. (3 and 2), *S. aureus* (1 and 4), *Corynebacterium* spp. (2 and 1), *Clostridium* spp. (1 and 1), *S. maltophilia* (1 and 1), *Streptococcus* spp. (2 in the meropenem group), *Corynebacterium jeikeium*, *Stomatococcus* sp., *Enterobacter* sp., and *Acinetobacter* sp. (1 each in the ceftazidime-plus-amikacin group).

discontinuation of protocol therapy (2 patients in each group), patient's withdrawal from study (2 patients in the ceftazidime-plus-amikacin group), and randomization but no treatment administered (1 patient in the ceftazidime-plus-amikacin group).

Thus, 958 patients (93% of the randomized cases) were evaluable in the intent-to-treat analysis for response to antibacterial therapy, including 483 in the monotherapy group and 475 in the combination group. At randomization, there were no significant differences between the two treatment groups in any characteristics of patients evaluable for response to therapy (Table 1). In particular, the groups were well balanced with respect to stratification by category of underlying disease, and more than 75% of the randomized patients (77% in the monotherapy group and 78% in the combination group) presented with leukemia or with lymphoma. The median duration times of neutropenia were 16 days for the meropenem group and 17 days for the ceftazidime-plus-amikacin group.

Response rates. The response rates were compared in an intent-to-treat analysis performed for the 958 patients. A successful outcome was reported for 270 (56%) of 483 patients in the meropenem group compared with 245 (52%) of 475 patients treated with ceftazidime plus amikacin ($P = 0.2$; 95% confidence interval for the difference between both response rates, -0.01 to 0.12) (Table 2). The distribution of the time to defervescence was estimated for each treatment group, and the two groups were compared by the log rank test (Fig. 1). A trend to a shorter time to defervescence was found in the monotherapy group ($P = 0.07$). However, the time to failure values of treatment regimen were similar for both groups, the median number of days to failure being 4 days (Fig. 2). The distributions of the causes of failure (213 patients treated with meropenem and 230 patients treated with ceftazidime-amikacin) were not statistically different between the treatment groups (Table 2).

Success rates were analyzed according to documentation of infection (Table 3). Among the 254 patients (27%) with microbiologically documented infections, 227 (24% of the total) presented with bacteremia which was due to multiple organisms in 28 patients and to single organisms in 199 patients. Of

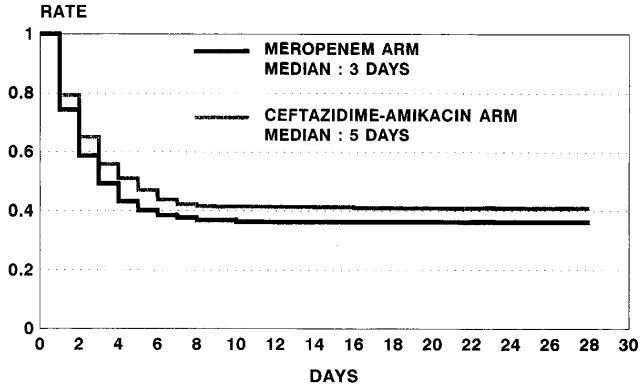

FIG. 1. Time to defervescence for all eligible patients by the logrank test ($P = 0.07$).

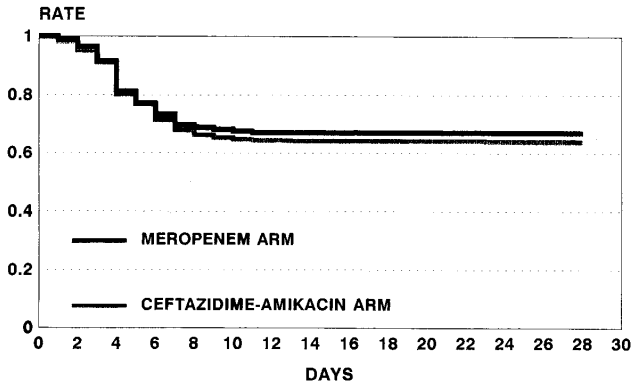

FIG. 2. Time to failure for all eligible patients by the logrank test (P = 0.39).

the latter, 138 (69%) had gram-positive bacteremia and 61 (31%) had gram-negative bacteremia. Coagulase-negative staphylococci were isolated most frequently, which was followed in frequency by viridans group streptococci, *Escherichia coli*, *Staphylococcus aureus*, and *P. aeruginosa*. While the numbers of bacteremias were similar in both groups, there was a slight imbalance in the distribution of bacteremic episodes between the two groups, with an excess of gram-positive bacteremias in the combination group and an excess of single gram-negative bacteremias in the monotherapy group; however, these differences did not reach statistical significance. The response rate in bacteremic patients was slightly higher in the monotherapy group (42%) than in the combination group (30%) (P = 0.09); these low success rates were mainly due to the poor efficacy of the regimens in single gram-positive bacteremias and in polymicrobial bacteremias, which together represented 67% of the bacteremic episodes in the meropenem group and 79% in the ceftazidime-plus-amikacin group. The success rate was higher in gram-negative bacteremias (70% in 37 patients treated with meropenem alone and 54% in 24 patients treated with ceftazidime plus amikacin [P = 0.31]) than in gram-positive bacteremias. Significant differences were not found by specific organisms, except for methicillin-sensitive coagulase-negative staphylococci, in which meropenem was more effective than ceftazidime plus amikacin (success in 9 of 10 versus 7 of 15, respectively; P = 0.04).

The initial regimen was stopped because of documentation of an organism resistant to the allocated beta-lactam in 41 of 125 patients (33%) treated with meropenem and in 44 of 129 patients (34%) treated with ceftazidime plus amikacin. The vast majority of the causative microorganisms which were resistant to the allocated beta-lactam were gram-positive microorganisms: coagulase-negative staphylococci (34 to meropenem and 33 to ceftazidime), *Enterococcus* spp. (3 to meropenem and 2 to ceftazidime), *S. aureus* (1 to meropenem and 4 to ceftazidime), *Corynebacterium* spp. (2 to meropenem and 1 to ceftazidime), *Clostridium* spp. (1 to meropenem and 1 to ceftazidime), *Streptococcus* spp. (2 to meropenem), *Corynebacterium jeikeium*, *Stomatococcus* spp. (1 strain of each resistant to ceftazidime). In addition, 4 gram-negative bacteria were resistant to the allocated beta-lactam and included the following: *Stenotrophomonas maltophilia* (1 to meropenem, 1 to ceftazidime), *Enterobacter* spp. and *Acinetobacter* spp. (1 strain of each resistant to ceftazidime).

Susceptibilities to meropenem, ceftazidime, and amikacin, respectively, were 56, 35, and 70% for coagulase-negative staphylococci; 96, 92, and 13% for viridans group streptococci; 100, 100, and 100% for *E. coli*; and 100, 100, and 75% for *P. aeruginosa*.

A total of 237 patients had clinically documented infections: 126 in the monotherapy group and 111 in the combination group. The observed response rates were similar in both groups (48 and 49%, respectively). The most frequent clinically documented infections were severe mucositis (higher than or equal grade 2 according to the World Health Organization definition) (n = 100), lower respiratory tract infections (n = 62), and cutaneous infections (n = 35).

Febrile episodes were classified as unexplained fever for 216 patients in the monotherapy group and 226 patients in the combination group. No significant differences in response rates

TABLE 3. Success rates by type of infection and infecting organism (intent-to-treat analysis)

Type or agent of infection	Value		P (confidence interval)[a]
	Meropenem (%)	Ceftazidime + amikacin (%)	
Overall	270/483 (56)	245/475 (52)	0.20 (−0.01–0.12)
Microbiologically documented infections	54/125 (43)	41/129 (32)	0.08 (−0.005–0.23)
Bacteremia	47/113 (42)	34/114 (30)	0.09 (−0.006–0.24)
Single gram-positive bacteremia	19/61 (31)	20/77 (26)	0.63 (−0.10–0.20)
Methicillin-susceptible CNS[b]	9/10	7/15	0.04
Methicillin-resistant CNS[b]	0/24	0/26	
S. aureus	0/1	3/10	
Streptococci	9/20 (45)	8/19 (42)	
Other gram-positive bacteria	1/6	2/7	
Single gram-negative bacteremia	26/37 (70)	13/24 (54)	0.31 (−0.09–0.41)
E. coli	10/14 (71)	11/16 (69)	
P. aeruginosa	5/8	0/0	
Klebsiella or *Enterobacter* spp.	2/2	0/3	
Other gram-negative bacteria	9/13	2/5	
Polymicrobial	2/15 (13)	1/13 (8)	
Nonbacteremic	7/12 (58)	7/15 (47)	
Clinically documented	61/126 (48)	54/111 (49)	0.93 (−0.13–0.13)
Unexplained fever	143/216 (66)	145/226 (64)	0.73 (−0.07–0.11)

[a] Confidence interval at 95% for the differences between both response rates (meropenem arm minus ceftazidime plus amikacin).
[b] CNS, coagulase-negative staphylococci.

TABLE 4. Analysis of efficacy (n = 894 patients)

Patient	Value	
	Meropenem	Ceftazidime + amikacin
Patients evaluable in ITT[a] analysis (no.)	483	475
Patients not evaluable (no.)	35	29
Treatment changed without adequate reason	19	21
Fever not related to infection	12	5
Viral or fungal infections	4	3
Evaluable patients (no.)	448	446
Response to the treatment (no.)		
Success[b]	258 (58%)	240 (54%)
Failure	190 (42%)	206 (46%)

[a] ITT, intent to treat.
[b] P = 0.29; confidence interval at 95% for the difference between both response rates, −0.03; 0.10.

were observed between the two groups (66 and 64%, respectively).

The addition of a glycopeptide was observed for 158 of 483 patients (33%) in the monotherapy group and for 182 of 475 patients (37%) in the combination group (P = 0.11). The most frequent reasons prompting this modification were persistence of fever (in 60 and 73 patients, respectively), documentation of resistant microorganisms (31 and 37 patients, respectively, for the primary infection and 4 and 5 patients, respectively, for further bacteremic infection), and progression of the primary infection (in 15 and 19 patients, respectively). The addition of empirical antifungal therapy did not differ between the monotherapy group (23%) and the combination group (25%).

The analysis was repeated after exclusion of patients for whom treatment was changed without adequate reason, including those with viral or fungal infections (assessed as failures in the intent-to-treat analysis) and those with fever not related to infections (assessed as successes in the intent-to-treat analysis). Thus, 448 patients were assessable for efficacy in the group treated with meropenem and 446 patients were assessable in the group treated with ceftazidime plus amikacin (Table 4). The success rates were similar (58 and 54%, respectively) in both treatment groups. In order to estimate the probability of success of the empiric therapy, data relative to 947 evaluable patients (11 had missing data) were fitted with a multivariate logistic regression model; the treatment arm was not a predictive factor of outcome.

Further infections. The occurrence of further infections, assessed for patients in whom the allocated regimen was not modified, did not differ between the two groups (56 of 483 [12%] patients in the monotherapy group compared with 58 of 475 [12%] patients in the combination group). Of the 25 further bacteremic infections (12 in the monotherapy arm and 13 in the combination group), 15 were due to single gram-positive organisms (8 and 7, respectively), 5 were due to single gram-negative rods (3 and 2, respectively), and 5 were polymicrobial (1 and 4, respectively).

There were no differences between the treatment groups with respect to the number of days to the development of a further infection (median of 7 days after randomization in the monotherapy group and 9 days in the combination group) or the number of patients with granulocyte counts of fewer than 100 cells per μl at the time of further infection documentation (41 of 56 in the meropenem group versus 34 of 58 in the ceftazidime-plus-amikacin group).

Mortality. At day 30, the overall mortality rate was 5% in both groups (24 cases in the monotherapy group and 22 in the combination group). Mortality due to the presenting infection or further infection was relatively uncommon. Eight patients in the monotherapy arm and 13 in the combination arm died from their presenting infections. Other causes of death included extensive cancer (6 patients in the meropenem group and 5 patients in the ceftazidime-plus-amikacin group, with infection in 3 and 4 cases, respectively), hemorrhage (3 and 1 patients, with infection in 2 and 1 patients, respectively), and other causes (in 7 and 3 patients, respectively). Five more deaths in the meropenem group and 7 in the ceftazidime-plus-amikacin group were reported after day 30. Death occurred at a median of 19 days (range, 1 to 54 days) after study entry in the meropenem group and at 15 days (range, 1 to 75 days) in the ceftazidime-plus-amikacin group.

Levels of amikacin in serum. Levels of amikacin in serum measured 8 h after the end of infusion were determined for 341 patients between days 2 and 4 and for 207 patients between days 5 and 7. The mean 8-h levels were 6.55 and 6.97 mg/liter, respectively. Regarding the first measurement, the mean 8-h amikacin serum level was 6.3 mg/liter for patients treated successfully, and it was 6.9 mg/liter for patients in whom the regimen failed. At the second measurement, the mean 8-h serum level was also higher for patients in whom the regimen failed (8 mg/liter) than the level recorded for patients treated successfully (6.6 mg/liter).

Adverse events. A total of 1,027 patients, including 830 adults (415 in both groups) and 197 children (101 in the meropenem group and 96 in the ceftazidime plus amikacin group), were evaluable for adverse events; 2 patients in the meropenem group and 5 in the ceftazidime-plus-amikacin group were not assessed for toxicity because they did not receive the regimen. Overall, the proportions of patients who developed adverse effects were similar in the two treatment groups (151 of 516 [29%] for meropenem; 148 of 511 [29%] for ceftazidime plus amikacin). However, only 19 patients (all adults) in the monotherapy arm and 31 (30 adults and 1 child) in the combination arm experienced an adverse event considered related or probably related to the study drug (P = 0.10). Moderate to severe nephrotoxicity probably attributable to the study regimen developed in 1 patient in the meropenem group and in 6 patients in the ceftazidime-plus-amikacin group (P = 0.07). Clinically relevant auditory toxicity was observed with 2 patients treated with the combination. Seven patients in each group developed a cutaneous allergic reaction. Hypokalemia related to the regimen was reported for 2 patients in the monotherapy arm and in 8 in the combination arm (P = 0.06). Gastrointestinal intolerance was very rarely associated with the allocated antibiotic regimen, since vomiting was reported for only 1 patient in each group and diarrhea was reported for 5 and 2 patients, respectively. The allocated regimen was discontinued because of toxicity in 3 patients given monotherapy and in 5 patients given the combination. Allergic reactions were the only reason for stopping the protocol antibiotic(s) (rash in 2 and 4 patients, respectively, and an anaphylactic-like reaction in 1 patient in each group).

DISCUSSION

The advent of broad-spectrum, bactericidal antibiotics such as carbapenems or extended-spectrum cephalosporins has raised the question of whether combination therapy can be safely replaced with monotherapy in granulocytopenic febrile cancer patients. Although several studies have suggested that monotherapy is sufficient in patients with possible infection or with short neutropenic periods (32), the answer to this ques-

tion has remained controversial especially for patients with bacteremia and for those with persistent and profound neutropenia. The present trial showed that meropenem monotherapy was as effective as the ceftazidime-plus-amikacin combination for the empiric treatment of fever in cancer patients with profound and persistent neutropenia.

Two analyses were performed: an intent-to-treat analysis including 93% of the randomized patients and a second analysis after removal of patients with fever not related to infection and those whose treatment was changed without adequate reason. Similar results were obtained in both analyses. It is interesting to note that the success rate observed in this trial for the combination group (53%) was similar to that obtained in the previous trial (54%) (6). The relatively low response rates observed for both groups are related to stringent definitions of failure which are supported by the IHS consensus; in particular, any change of the allocated regimen was assessed as a failure (19). As noted in other recent trials (8, 17), adjustment of therapy has become a common clinical practice in granulocytopenic cancer patients with persistent fever despite the absence of a clinical deterioration or of the documentation of a microorganism resistant to the allocated regimen. In the present study, the most frequent modification was the addition of a glycopeptide which occurred in 35% of the overall population and which was justified by documentation of a resistant microorganism in only 7%. Thus, a glycopeptide was added empirically in 28% of the randomized patients, mainly in those with persistent fever. Although this practice is common in granulocytopenic cancer patients, no study has demonstrated its benefit.

The rationale for using a beta-lactam–aminoglycoside combination is based mainly on three arguments: rapid bactericidal effect, enhanced killing afforded by synergism, and reduction in the emergence of resistance (11). Regarding the first argument, the rapid bactericidal effect of the aminoglycoside might be associated with faster defervescence; however, in the present trial, the time to defervescence was similar in both groups. Regarding the second argument, the enhanced killing afforded by synergism might be beneficial in the two following circumstances: gram-negative bacteremia and streptococcal bacteremia. Indeed, several papers published more than 20 years ago (23–26) showed that the outcome of cancer patients with gram-negative bacteremia was significantly improved when treatment consisted of combination antibiotics synergistic in vitro against the offending pathogen, compared with nonsynergistic combinations. De Jongh et al. (7) confirmed these observations in patients with severe (fewer than 100 neutrophils per mm^3) and persistent neutropenia. Although the number of patients in the present trial with gram-negative bacteremia was low, meropenem monotherapy was as effective as the combination in this subgroup of patients, and the response rate (26 of 37 = 70%) was comparable to that observed in the previous trial with the combination of piperacillin/tazobactam plus amikacin (18 of 24 = 75%) (6). Similarly, since synergism between extended-spectrum cephalosporins and aminoglycosides was observed in a rat model of streptococcal endocarditis (15), a similar benefit might have occurred in granulocytopenic patients with streptococcal bacteremia in the combination group. However, the response rate was not higher in the combination group (42% compared with 45% in the monotherapy group). The low efficacy of both regimens in streptococcal bacteremia was not related to beta-lactam-resistant strains, since 24 of the 25 viridans group streptococci tested were susceptible to the allocated beta-lactam. Again, this was mainly due to the addition of a glycopeptide because of persistent fever.

The third argument for combining aminoglycosides with beta-lactam antibiotics in the treatment of severe infections is the prevention of emergence of resistant strains. Only one study performed in patients with severe infections (18) has shown that patients treated with a carboxypenicillin plus an aminoglycoside presented a lower likelihood of emergent resistant isolates than patients treated with piperacillin alone. Although this observed difference was possibly due to the addition of the aminoglycoside, the choice of the penicillin might have been important. Another study (5) comparing imipenem/cilastatin alone to imipenem/cilastatin plus netilmicin for the treatment of severe infections did not confirm this concept, since it showed that the addition of netilmicin did not prevent the emergence of imipenem-resistant *P. aeruginosa*. In addition, the numbers of patients who acquired an imipenem-resistant microorganism during the administration of imipenem or imipenem plus netilmicin were similar in both groups (22). In the present trial, colonization with microorganisms resistant to the allocated beta-lactam was not studied, but the numbers of further bacteremic infections did not differ between the monotherapy group and the combination group. In addition, the numbers of microorganisms resistant to the allocated beta-lactam isolated from patients with further bacteremia were similar for both groups.

A secondary objective of this study was the comparison of the success rates of both regimens in patients with single gram-positive bacteremia. Although this trial did not enroll the expected number of documented gram-positive bacteremic episodes, we can conclude that meropenem alone was not superior to ceftazidime plus amikacin for patients with single gram-positive bacteremia (19 of 61 [31%] versus 20 of 77 [26%] patients treated successfully, respectively). The lack of a difference associated with the use of meropenem is certainly related to the high proportion of methicillin-resistant staphylococci that caused 37% of the single gram-positive bacteremic episodes assessed as failures (41% in the meropenem group and 34% in ceftazidime-plus-amikacin combination group). However, a significantly better outcome was observed in patients with bacteremia due to methicillin-susceptible staphylococci treated with meropenem.

The addition of an aminoglycoside is associated with increased costs and is potentially toxic. In view of data obtained in a previous trial (20) showing that a large single daily dose of amikacin was not more toxic than multiple smaller daily doses, amikacin was administered in a single daily dose. The rate of nephrotoxicity, which was very low in this study (less than 1%), was slightly higher in the combination group than in monotherapy group ($P = 0.07$). In the previous trial that assessed the safety of the single daily dose, audiograms in 144 patients showed a 9% incidence of auditory toxicity. In the present trial, no monitoring with audiograms was planned; only 2 patients who were receiving ceftazidime plus amikacin developed auditory toxicity. If the rates of nephrotoxicity and ototoxicity probably related to the study drugs were taken together, ceftazidime plus amikacin appeared significantly more toxic than meropenem alone ($P = 0.03$). No seizure was observed, and the other adverse events were mild. In particular, unlike the patients given high doses of imipenem/cilastatin in the study by Freifeld et al. (17), the patients treated with meropenem in this trial did not develop gastrointestinal intolerance or pseudomembranous colitis.

In summary, the present study confirms that meropenem alone is as effective as ceftazidime plus amikacin for the empiric treatment of fever in persistently granulocytopenic cancer patients. The overall response rates, which were relatively low in both groups, were related to stringent definitions of failure

and were not associated with high mortality. Both regimens were well tolerated.

ACKNOWLEDGMENTS

This work was supported by a grant from Zeneca Pharmaceuticals, Macclesfield, United Kingdom. The GIMEMA group was supported in part by a grant from Consiglio Nazionale delle Ricerche (CNR) Progetto ACRO (contract nos. 94.01122 PF 39 and 94.01163 PF 39). C. Viscoli was in part supported by a grant from CNR Progetto ACRO (contract no. 95.00597 PF39).

REFERENCES

1. **Barry, A. L., and C. Thornsberry.** 1991. Susceptibility tests: diffusion test procedures, p. 1117–1125. *In* A. Balows and W. J. Hausler (ed.), Manual of clinical microbiology, 5th ed. American Society for Microbiology, Washington, D.C.
2. **Blaser, J., C. König, R. Fatio, F. Follath, A. Cometta, M. Glauser, and The International Antimicrobial therapy Cooperative Group of the EORTC.** 1995. Multicenter quality control study of amikacin assay for monitoring once-daily dosing regimens. Ther. Drug Monit. **17:**133–136.
3. **Breitmann, L. E.** 1991. Confidence intervals assess both clinical significance and statistical significance. Ann. Intern. Med. **14:**515–517.
4. **Calandra, T., and A. Cometta.** 1991. Antibiotic therapy for gram-negative bacteremia. Infect. Dis. Clin. N. Am. **5:**817–834.
5. **Cometta, A., J. D. Baumgartner, D. Lew, W. Zimmerli, D. Pittet, P. Chopart, U. Schaad, C. Herter, P. Eggimann, O. Huber, B. Ricou, P. Suter, R. Auckenthaler, R. Chiolero, J. Bille, C. Scheidegger, R. Frei, and M. P. Glauser.** 1994. Prospective randomized comparison of imipenem monotherapy with imipenem plus netilmicin for treatment of severe infections in nonneutropenic patients. Antimicrob. Agents Chemother. **38:**1309–1313.
6. **Cometta, A., S. Zinner, R. de Bock, T. Calandra, H. Gaya, J. Klastersky, J. Langenaeken, M. Paesmans, C. Viscoli, M. P. Glauser, and The Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer.** 1995. Piperacillin-tazobactam plus amikacin versus ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. Antimicrob. Agents Chemother. **39:**445–452.
7. **De Jongh, C. A., J. H. Joshi, and K. A. Newman.** 1986. Antibiotic synergism and response in gram-negative bacteremia in granulocytopenic cancer patients. Am. J. Med. **80**(Suppl. 5C)**:**96–100.
8. **De Pauw, B. E., S. C. Deresinsky, R. Feld, E. F. Lane-Allman, J. P. Donnelly, and The Intercontinental Antimicrobial Study Group.** 1994. Ceftazidime compared with piperacillin and tobramycin for the empiric treatment of fever in neutropenic patients with cancer. Ann. Intern. Med. **120:**834–844.
9. **Dixon, W. J., M. B. Brown, L. Engelman, and R. I. Jeinrich.** 1994. BMDP statistical analysis software. University of California, Berkeley.
10. **Edwards, J. R., P. J. Turner, and C. Wannop.** 1989. In vitro antibacterial activity of SM-7338, a carbapenem antibiotic with stability to dehydo-peptidase-1. Antimicrob. Agents Chemother. **32:**215–222.
11. **Eliopoulos, G. M., and C. T. Eliopoulos.** 1988. Antibiotic combinations: should they be tested? Clin. Microbiol. Rev. **1:**139–156.
12. **EORTC International Antimicrobial Therapy Cooperative Group.** 1987. Ceftazidime combined with a short or long course of amikacin for empirical therapy of gram-negative bacteremia in cancer patients with granulocytopenia. N. Engl. J. Med. **317:**1692–1698.
13. **EORTC International Antimicrobial Therapy Cooperative Group.** 1991. Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. J. Infect. Dis. **163:**951–958.
14. **EORTC International Antimicrobial Therapy Cooperative Group.** 1993. In vitro activity of piperacillin/tazobactam against 365 aerobic bacteria isolated from blood in granulocytopenic cancer patients, p. 186. *In* Program and abstracts of the 18th International Conference on Chemotherapy. Scandanavian Society for Antimicrobial Chemotherapy, Stockholm.
15. **Francioli, P., and M. P. Glauser.** 1993. Synergistic activity of ceftriaxone combined with netilmicin administered once daily for treatment of experimental streptococcal endocarditis. Antimicrob. Agents Chemother. **37:**207–212.
16. **Freedman, L. S., and S. J. White.** 1976. On the use of Pocock and Simon's method for balancing treatment numbers over prognostic factors in the controlled clinical trial. Biometrics **32:**691–694.
17. **Freifeld, A. G., T. Walsh, D. Marshall, J. Gress, S. M. Steinberg, J. Hathorn, M. Rubin, P. Jarosinsky, V. Gill, R. C. Young, and P. A. Pizzo.** 1995. Monotherapy for fever and neutropenia in cancer patients: a randomized comparison of ceftazidime versus imipenem. J. Clin. Oncol. **13:**165–176.
18. **Gribble, M. J., A. W. Chow, S. C. Naiman, J. A. Smith, W. R. Bowie, S. L. Sacks, L. Grossman, N. Buskard, G. H. Growe, and L. H. Plenderleith.** 1983. Prospective randomized trial of piperacillin monotherapy versus carboxypenicillin-aminoglycoside combination regimens in the empirical treatment of serious bacterial infections. Antimicrob. Agents Chemother. **24:**388–393.
19. **Immunocompromised Host Society.** 1990. The design, analysis, and reporting of clinical trials on the empirical antibiotic management of the neutropenic patient. J. Infect. Dis. **161:**397–401.
20. **International Antimicrobial Therapy Cooperative Group of the EORTC.** 1993. Efficacy and toxicity of single daily dose of amikacin and ceftriaxone versus multiple daily doses of amikacin and ceftazidime for infection in patients with cancer and granulocytopenia. Ann. Intern. Med. **119:**584–593.
21. **Isenberg, H. D., J. A. Washington, G. V. Doern, and D. Amsterdam.** 1991. Specimen collection and handling, p. 2–15. *In* A. Balows and W. J. Hausler, Jr., K. L. Herrmann, H. D. Isenberg, and H. J. Shadomy (ed.), Manual of clinical microbiology, 5th ed. American Society for Microbiology, Washington, D.C.
22. **Iten, A., A. Cometta, P. Eggimann, H. Siegrist, and P. Francioli.** 1992. The addition of netilmicin (NET) to imipenem (IMIP) does not prevent the emergence of bacteria resistant (R) to IMIP during treatment (ttt) of severe infections, p. 198. *In* Program and abstracts of the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
23. **Klastersky, J., R. Cappel, and D. Daneau.** 1972. Clinical significance of in vitro synergism between antibiotics in gram-negative infections. Antimicrob. Agents Chemother. **2:**470–474.
24. **Klastersky, J., R. Cappel, and D. Daneau.** 1974. Antibacterial activity in serum and urine as a therapeutic guide in bacterial infections. J. Infect. Dis. **129:**187–190.
25. **Klastersky, J., F. Meunier-Carpentier, and J.-M. Prevost.** 1977. Significance of antimicrobial synergism for the outcome of gram-negative sepsis. Am. J. Med. Sci. **273:**157–161.
26. **Klastersky, J., and S. H. Zinner.** 1982. Synergistic combinations of antibiotics in gram-negative bacillary infections. Rev. Infect. Dis. **4:**294–298.
27. **Leyland, M. J., K. F. Bayston, J. Cohen, R. Warren, A. C. Newland, A. J. Bint, C. Cefai, D. G. White, S. A. Murray, D. Bareford, and N. B. Deaney.** 1992. A comparative study of imipenem versus piperacillin plus gentamicin in the initial management of febrile neutropenic patients with haematological malignancies. J. Antimicrob. Chemother. **30:**843–854.
28. **Liang, R., R. Yung, E. Chiu, P. Y. Chau, T. K. Chan, W. K. Lam, and D. Todd.** 1990. Ceftazidime versus imipenem-cilastatin as initial monotherapy for febrile neutropenic patients. Antimicrob. Agents Chemother. **34:**1336–1341.
29. **Nie, N. H., C. H. Hull, J. G. Jenkins, K. Steinbrenner, D. H. Bent, and H. J. Norusis.** 1988. Statistical package for the social sciences. SPSS, Inc., Chicago.
30. **Pizzo, P. A.** 1993. Management of fever in patients with cancer and treatment-induced neutropenia. N. Engl. J. Med. **328:**1323–1332.
31. **Pizzo, P. A.** 1995. Empirical therapy and prevention of infection in immunocompromised host, p. 2686–2696. *In* G. L. Mandell, J. E. Bennett, and R. Dolin (ed.), Principles and practice of infectious diseases. Churchill Livingstone, Inc., New York.
32. **Pizzo, P. A., J. W. Hathorn, J. Hiemenz, M. Browne, J. Commers, and D. Cotton.** 1986. A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. N. Engl. J. Med. **315:**552–558.
33. **Pocock, S. J.** 1983. Monitoring trial progress, p. 142–159. J. Wiley and Sons, New York.
34. **Rolston, K. V. I, P. Berkey, G. P. Bodey, E. J. Anaissie, N. M. Khardori, J. H. Joshi, M. J. Keating, F. A. Holmes, F. F. Cabanillas, and L. Elting.** 1992. A comparison of imipenem to ceftazidime with or without amikacin as empiric therapy in febrile neutropenic patients. Arch. Intern. Med. **152:**283–291.
35. **Sahm, D. F., and J. A. Washington.** 1991. Antibacterial susceptibility tests: dilution methods, p. 1105–1116. *In* A. Balows and W. J. Hausler, Jr., K. L. Herrmann, H. D. Isenberg, and H. J. Shadomy (ed.), Manual of clinical microbiology, 5th ed. American Society for Microbiology, Washington, D.C.
36. **Schimpff, S., W. Satterlee, V. M. Young, and A. Serpick.** 1971. Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. N. Engl. J. Med. **284:**1061–1065.
37. **The Meropenem Study Group of Leuven, London and Nijmegen.** 1995. Equivalent efficacies of meropenem and ceftazidime as empirical monotherapy of febrile neutropenic patients. J. Antimicrob. Chemother. **36:**185–200.
38. **Wade, J., C. I. Bastamante, A. Devlin, R. Finley, G. Drusano, and B. Thomson.** 1987. Imipenem versus piperacillin plus amikacin, empiric therapy for febrile neutropenic patients: a double blind trial. Program and Abstract of the 27th Interscience Conference on Antimicrobial Agent and Chemotherapy (Abstract)
39. **Winston, D. J., H. Winston, D. A. Bruckner, and R. E. Champlin.** 1991. Beta-lactam antibiotic therapy in febrile granulocytopenic patients. A randomized trial comparing cefoperazone plus piperacillin, ceftazidime plus piperacillin, and imipenem alone. Ann. Intern. Med. **115:**849–859.