Imipenem/Cilastatin versus Cefepime as Empiric Monotherapy for Fever in Neutropenic Patients after Hematopoietic Stem Cell Transplantation

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Abstract
Objective: To evaluate the potential advantages of imipenem/cilastatin in control of fever in neutropenic HSCT recipients.
Patients and Method: In this single-center study, 111 consecutive febrile episodes in 104 neutropenic HSCT recipients with a mean age of 26 years were randomized to treatment either with Imipenem/cilastatin 1 g, IV, q8h or cefepime (our standard regimen) 2 g, IV, q8h. If fever persisted, sequential antibiotics were added in 72-hour intervals: vancomycin, amikacin and amphotericin-B. The study population was at serious risk of a poor outcome, since 73.5% of febrile episodes occurred after allogeneic and 26.5% of febrile events occurred after autologous hematopoietic stem cell transplantation.
Results: The median total duration of neutropenia was 10 days, and the median leukocyte count at study inclusion was 0.16×10^9/l. The two patient groups were comparable in terms of Age, gender, underlying disease, conditioning regimen, clinical and bacterial documentation, severity and duration of neutropenia and mucositis, GI decontamination and G-CSF administration. Bacteremia was found in 20.6%, other microscopically documented infections in 9.8%, clinically documented infections in 20.6% and fever of unknown origin in 49% of the febrile episodes. Most (102) febrile episodes were evaluable for response. No significant difference was found between imipenem/cilastatin and cefepime in terms of success rate (73.1% versus 62%), empirical addition of vancomycin (38% versus 26.2%) or median duration of antibiotic therapy (7 days in both).The difference between imipenem/cilastatin and cefepime was statistically significant for median duration of fever (1.5 versus 2 days) and median time of resolution of neutropenia (12 versus 14 days). The overall response rates to initial monotherapy was significantly higher for HSCT recipients with thalassemia, MM, lymphoma, AA, than recipients with ALL, AML, CML, CLL ($P<0.001$) and for episodes of fever of unknown origin than episodes of clinically documented infections (87.8% versus 12.2%). In episodes of success without modification, the median duration of neutropenia before entry was longer than episodes when vancomycin was added ($P<0.027$).No patient died from the infection. Both antibiotic regimens were well tolerated. The study treatment being stopped only in 1 patient because of toxicity (cutaneous allergy to imipenem/cilastatin).
Conclusions: Imipenem/cilastatin and cefepime are effective and well tolerated when used as initial empirical treatment for HSCT recipient with prolonged neutropenia. But imipenem/cilastatin may be more effective than cefepime, as evidenced by a significantly better response in two outcome measures and in one subgroup of patients (AML).
Key words: Febrile neutropenia Monotherapy Hematopoietic stem cell transplantation Randomized trial.

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Introduction
Infections contribute significantly to the morbidity and mortality associated with autologous and allogeneic hematopoietic stem cell transplantation (HSCT). Patients undergoing HSCT are at risk for infectious complications because of several factors.[22] The patients will experience a prolonged period of neutropenia, which makes them susceptible to a variety of infections. Immunosuppression used in allogeneic transplantation may further increase patients' risk for infection beyond the period of granulo-

cytopenia and may last for 12–24 months post transplant. This period represents the time necessary for immune reconstitution to occur. Complications such as graft-versus-host disease (GVHD) may also further prolong the period of risk of infection.[7,3]

Treatment of fever in the neutropenic transplant recipients requires strategies similar to the ones that have been effective in patients with leukemia. Broad spectrum antibacterial coverage should be initiated early.

Infections are commonly caused by Gram-negative aerobic bacteria (such as Pseudomonas aeruginosa and enterobacteriaceae) and Gram-positive cocci (such as enterococci, streptococci and staphylococci), which should be covered by empiric first-line antibiotic therapy. Less frequently, infections are caused by fungi and anaerobic bacteria, and initial therapy does not necessarily have to cover coagulase-negative staphylococci, oxacillin-resistant S. aureus (MRSA), anaerobic bacteria and fungi [12].

Several studies have shown no striking differences between monotherapy and multidrug combinations for empirical treatment of uncomplicated episodes of fever in neutropenic patients. A third- or fourth-generation cephalosporin (ceftazidime or cefepime) or a carbapenem (imipenem-cilastatin or meropenem) may be used successfully as monotherapy. Cefepime, imipenem-cilastatin, and meropenem, unlike ceftazidime, have excellent activity against viridans streptococci and pneumococci. Vancomycin was shown to be required less frequently with cefepime than with ceftazidime monotherapy.[15,23]

Imipenem/cilastatin is a carbapenem with broad antimicrobial spectrum including Pseudomonas aeroginosa and most other gram-negative bacteria. It has excellent activity against anaerobic and gram-positive organisms including streptococci. Cefepime is a new cephalosporin with a broader spectrum of activity against Gram-negative organisms than ceftazidime and other extended-spectrum cephalosporins. It is also more active than third-generation cephalosporins against Gram-positive cocci, such as Streptococcus pneumoniae and most other streptococcal species, as well as staphylococcal species. A broad and potent spectrum of activity, together with advanced pharmacological properties (e.g. long elimination half-life), make cefepime a suitable antibiotic for initial empirical therapy for febrile episodes in neutropenic patients.[6, 8, 21, 18]
In this randomized trial, we study only HSCT recipients with long duration of neutropenia. The aim of this prospective randomized study was to evaluate and to compare the efficacy and safety and tolerance of imipenem/cilastatin and cefepime as empirical monotherapy in HSCT recipient with prolonged neutropenia.

Patients and method

Study design and criteria for eligibility

This open, comparative, single blinded, randomized, single-centre study was conducted in four BMT wards in hematology oncology and BMT research center of Shariati hospital. The trial was designed in accordance with guidelines issued by the Infectious Diseases Society of America (IDSA; 2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer).

Patients who had undergone hematopoietic stem cell transplantation were evaluated for enrolment.Patients that were eligible for study participation if they had fever attributable to neutropenia and presumed infection. Fever was defined as an oral temperature 38°C on two occasions at least 1 h apart or 38.5°C on one occasion. Neutropenia was defined as an absolute neutrophil count of $<0.5 \times 10^9$/L or if $>1 \times 10^9$/L, expected to fall below 0.5×10^9/L within 24–48 h because of preceding chemotherapy. Only patients with presumed infectious causes of fever were included in the trial. Patients were excluded if they met any of the following criteria: known allergy to any of the study antibiotics (cefepime, imipenem/cilastatin, amikacin, vancimycin) or history of ß-lactam allergic reactions, serum creatinine level >1.5 mg/dL or creatinine clearance <40 mL/min, concomitant treatment with an iv antibiotic or administration of an iv antibiotic within 96 h before study entry. Patients receiving oral antibacterial prophylaxis, such as co-trimoxazole and metronidazole, were allowed to participate in the study.

Ethics

The trial was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee.

Randomization procedure: Patients were randomly allocated to one of the arms of the trial,

stratified by centre, according to a computer-generated random-number program. A correct balance between the treatment arms was ensured by randomly permuted blocks. Successive neutropenic episodes allowed subsequent randomization of the same patient.

Therapeutic regimens

Patients were randomly allocated to one of the arms of the trial. Patients received intravenously either imipenem/cilastatin (1 gr / TDS or 50 mg/kg/d in 3 or 4 divided doses if wt< 40kg) or cefepime (2 gr / TDS or 50mg/kg/TDS if wt< 40kg). If no infection was identified after 3 days of treatment, the neutrophil count was ≥500 cells/mm^3 for 2 consecutive days, and the patient was afebrile for ≥48 h, antibiotic therapy may be stopped at that time(antibiotic treatment should be continued for a minimum of 7 days). If no infection was identified after 3 days of treatment, and the patient was afebrile for ≥48 h, but the neutrophil count was <500 cells/mm^3 administration of antibiotics throughout the neutropenic period was continued. In patients who remained febrile after 72 h, antibiotic therapy was modified as part of a multistep strategy by successive addition of vancomycin (1 gr /BD or 40 mg/kg/d in 4 divided doses if wt< 40kg), (vancomycin considered if any of the criteria for use of vancomycin have occurred).In persistent fever after 2 days of vancomycin administration, no identified infection and no change in patients condition vancomycin was discontinued and third line regimen was begun (Amikacin, 500 mg/BD or 15 mg/kg/d in 2 divided doses).Antifungal therapy was also started if the patient remained febrile or if their clinical status worsened after 4–6 days of antibiotic therapy (0.5-0.7 mg/kg/d, max 1-1.5 mg/kg).

In patients with a microbiologically documented infection (MDI), therapy was modified, if necessary, to provide optimal treatment with minimal adverse effects and lowest cost, but broad-spectrum coverage maintained to prevent breakthrough bacteremia. Antibiotic treatment continued for a minimum of 7 days or until culture results indicated that the causative organism has been eradicated, infection at all sites has resolved, and the patient is free of significant symptoms and signs.

Clinical and laboratory evaluation: A complete medical history and physical examination, as well as a complete blood cell and differential count, routine chemistry, at least two sets of blood cultures were obtained from two different sites and a chest X-ray was performed whenever signs or symptoms of respiratory tract abnormality was present. One set of blood culture consisted of two bottles with 10 ml of blood added to each. Cultures of any other sites of infection were performed as clinically indicated.

Patients were monitored daily for clinical signs and symptoms and intercurrent events during antibiotic treatment. Complete blood cell counts, coagulation and chemistry parameters, and urinalysis were performed at least three times a week. Microbiological specimens were obtained before and during therapy, as clinically indicated. Blood cultures were obtained daily from patients with persistent fever; in patients with established bacteraemia, blood cultures were repeated until negative results.

Bacterial isolates were not tested for *in vitro* susceptibility to cefepime, imipenem/cilastatin and amikacin by the Kirby–Bauer disc diffusion method or by determination of MICs as recommended by the NCCLS.

Classification of febrile episodes

Primary febrile episodes were classified according to guidelines issued by the IHS consensus conference and the ESCMID as follows: (i) MDI with or without bacteraemia; (ii) clinically documented infection (CDI); (iii) fever of unknown origin (FUO); and (iv) non-infectious fever. Single blood culture isolates were sufficient to classify an episode as bacteraemic, except for coagulase-negative staphylococci (CoNS) and *Corynebacterium* spp. other than *Corynebacterium jeikeium*, which required at least two positive blood culture specimens.

Evaluation of response

Response was assessed both at 72 h (early evaluation) and at completion of therapy (overall evaluation). Response was categorized as a success without modification if all of the following criteria were met: afebrile (<38°C) for 4 consecutive days, clearance of signs and symptoms of infection, infecting microorganism eradicated (whenever isolated) and no recurrence of the primary infection within 1 week after treatment completion and success with modification if patient needed addition or modification of first line regimen for defervescence. Failure was defined as death from primary in-

fection. A patient was considered non-assessable for response in the following circumstances: (i) co-existent fungal or viral infection; (ii) febrile episode not related to infection; and (iii) protocol violation (e.g. non-adherence to protocol; early discontinuation secondary to severe adverse effects).

Toxicity

Toxicity was graded according to the World Health Organization (WHO) grading system. Nephrotoxicity was defined as an increase in serum creatinine by at least twice the upper limit of normal. Hepatotoxicity was assessed on the basis of transaminase, bilirubin and alkaline phosphatase levels; abnormal values were defined as 1.5–2 times above the baseline value and normal range.

Statistical analysis

All data were entered in a computerized data base and analyzed by a statistical program using ANOVA analysis. Statistical significance was assessed by the Chi-square test and fisher's exact test.

Results

Characteristics of the study population

From April to September 2005, a total of 111 episodes of febrile neutropenia occurring in 102 patients who had undergone hematopoietic stem cell transplantation from 4 BMT wards in hematology oncology and BMT research center of Shariati hospital were randomized into the study. Nine episodes were not eligible (5 imipenem/cilastatin, 4 cefepime). The reasons were (imipenem/cilastatin, cefepime), protocol violation (2/2), early discontinuation of protocol therapy due to allergic reaction (1/0), and noninfectious fever (2/2). Thus, 102 febrile episodes were evaluable for response, 52 in imipenem/cilastatin and 50 in cefepime group.

Demographic and baseline medical characteristics were well balanced between the two treatment groups (Table 1). All patients had undergone stem cell transplantation (73.5% after allogeneic stem cell transplantation and 26.5% after autologous stem cell transplantation). The median leukocyte at entry was 0.16×10^9 cells/L. The median duration of neutropenia (leukocyte count$<1.0\times 10^9$ cells/L) before entry was 3 days. The leukocyte had increased to over 1.0×10^9 cells/L by a median of 6 days. The median time of fever after HSCT was 6 days. Prophylactic G-CSF was administered in 43(43.1%) febrile episodes. Amphotericin B were administered in 68(76.5%) of febrile episodes (51% before entry and 25.5% after entry), with mean leukocyte count of 0.433×10^9/L. Mucositis occurred in 54.9% with the median time of 2 days before HSCT. The median time of occurance of GVHD after HSCT was 9.7 days.

Acyclovir was administered at the dose of 15 mg/kg/day intravenously starting on day 1 and switched to oral by day 14. This was continued for 3–6 months as herpes simplex virus (HSV) prophylaxis.

Sulfamethoxazole/Trimethoprim for Pneumocystis carinii prophylaxis was started from administration day till transplantation. GVHD prophylaxis consisted of Cyclosporine (3 mg/kg/ day i.v.) administered from 3 days before HSCT then 10 mg/kg/day po. Methotrexate was administered on days 1, 3, 6 and 11 post BMT followed by folinic acid rescue. All patients had IV catheter in situ. The patients' characteristics, (age, gender, underlying disease, graft type, mucositis occurrence and the degree of chemotherapy-induced mucositis, duration of neutropenia, G-CSF and amphotericin B administration) were well balanced with no statistical difference between the two treatment arms (Table 1).

Clinical and microbial characteristic of infections

There were no significant differences between the two treatment groups in the occurrence of any type of febrile episode according to clinical and microbiological records. Of 102 febrile episodes, bacteremia occurred in 20(20.6%), that being single pathogen bacteremia. Gram-positive microorganisms were responsible for 70% and gram-negative bacilli for 30% of the bacteremic episodes. CoNS were the most common Gram-positive organisms, isolated in 71% of bacteraemic episodes, and *Escherichia coli* was the most common Gram-negative organism, isolated in 83% of these bacteraemic cases. The pathogens causing bloodstream infections are shown in table 2.

Microbiologically documented infections (MDI) without bacteremia were found in 10(9.8%) of febrile episodes (imipenem/ cilastatin 5, cefepime 5). 12 of these were urinary tract infections, mainly caused by E.coli [7, 11].

Table 1- Characteristic of 102 febrile episodes (No statistically differences between two groups).

	Imipenem/cilastatin		Cefepime		Total	
	n	(%)	n	(%)	n	(%)
Eligible febrile episodes	52	(51)	50	(49)	102	(100)
Mean age of patients(years)	26.2	(range: 5-60)	26.8	(range: 4-58)	26	(range: 4-60)
Male/female	24/28	(46.2/53.8)	23/27	(46/54)	47/55	(47/54)
Underlying disease						
AML	13	(25)	11	(22)	24	(23.5)
ALL	9	(17.3)	11	(22)	20	(19.6)
CML	8	(15.4)	4	(8.5)	12	(11.8)
CLL	2	(3.6)	2	(4.3)	4	(3.9)
MDS	1	(1.9)	0	(0)	1	(1)
AA	7	(13.5)	3	(6.4)	10	(9.8)
FA	2	(13.8)	0	(0)	2	(2)
HD	2	(13.8)	2	(4.3)	4	(3.9)
NHL	1	(1.9)	2	(4.3)	3	(2.9)
MM	5	(9.6)	8	(16)	13	(12.7)
Thalassemia I,II	1	(1.9)	3	(6)	4	(3.9)
Thalassemia II	1	(1.9)	4	(8)	5	(4.9)
Allogenic	42	(80.8)	33	(66)	75	(73.5)
Autologous	10	(19.2)	17	(34)	27	(26.5)
Duration of neutropenia before entry(days)	4		3		3	
Time of fever(days)	6		6.5		6	
WBC at entry($\times 10^9$/l)	0.15		0.20		0.16	
Defervescence(days)	9		9.5		9.5	
Prophylactic G-CSF	21	(40.4)	23	(46)	44	(43.1)
Duration of neutropenia before G-CSF(days)	4.9		3.7		4.3	
WBC at time of G-CSF administration($\times 10^9$/l)	0.190		0.35		0.30	
Amphotericin administration day	5.6		5.4		5.5	
WBC at amphotericin ($\times 10^9$/l)	0.322		0.586		0.451	
AmphotericinB administration	42	(84)	36	(72)	78	(76.5)
before entry	26	(52)	26	(52)	52	(51)
after entry	16	(32)	10	(20)	26	(25.5)
Mucositis day	6		6		6.1	
Occurance of mucositis	34	(65.4)	22	(44)	56	(54.9)
before entry(days)	1		2		2	

A total of 22 episodes (21.5%) were categorized as CDI (imipenem/cilastatin 11, cefepime11). The most frequent sources of infection was mucous membrane (9%), lower respiratory tract (7%), skin and soft tissues, including catheter tunnel infections (5%), and perianal infections(4%).

Fever of unknown origin (FUO) occurred in 50 (49%) of the febrile episodes (imipenem/ cilastatin 27, cefepime 23).

Four infections were caused by nonbacterial pathogens .Of 4 febrile episodes not related to infection, 2 were caused by G-CSF and 2 by red blood cell transfusion.

Response rate and outcome

102 febrile events were evaluable for response (Table 3). Overall Success without modification occurred in 67.6% of the febrile episodes, 73.1% in the imipenem/cilastatin group, 62% in the cefepime group. Vancomycin was added following defined criteria in 14 (26.9%) and 19 (38%) of episodes. The success rate in infections with bacteremia were 5 of 6 (83.3%) and 6 of 9 (66.7%), respectively (P>0.05). The success rate in Gram-positive infections treated with vancomycin was 2 of 2 in the imipenem/ cilastatin group and 3 of 3 in the cefepime group. For bacteriologically confirmed episodes, the overall response rate was 83.3% for imipenem/cilastatin, compared with 66.7% for cefepime. The response rate achieved by the 2 regimens (imipenem/cilastatin, cefepime) in single-agent, gram-positive and gram-negative bacteremia was similar. The observed success

Table 2- Microbiologic characteristic of febrile episodes

Identified source	Total	Imipenem/cilastatin	Cefepime
Gram-positive bacteremia	14	5	9
S.aureus	4	0	4
S.epidermis	10	5	5
Strep.spp	0	0	0
Enterococcus	0	0	0
Gam-negative bacteremia	6	4	2
E.coli	5	3	2
Klebsiella	0	0	0
p.aeroginosa	0	0	0
Enterobacter	0	0	0
Acinetobacter	1	1	0
MDI	15	7	8
UTI	12	6	6
GI infection	2	1	1
Others	1	0	1
UTI	12	6	6
E.coli	7	3	4
Klebsiella	0	0	0
Acinetobacter	3	2	1
Strep.spp	2	1	1
Gr-/gr+ ratio	0.43	0.80	0.22
systemic invasive mycosis	0	0	0

rates in CDIs were 36.4% and 20% respectively. For fever of unknown origin (FUO), the overall response rate was 89.9% for imipenem/cilastatin, compared with 82.6% for cefepime. The rate of successful clinical response was higher for imipenem/cilastatin than for cefepime, for all episodes with no statistical difference.

Imipenem/cilastatin was significantly more effective than cefepime in patients who had AML. Again, the difference between groups in clinical response was largely attributable to a greater number of completely cured episodes in the imipenem/cilastatin group relative to the cefepime group (84.6% vs 27.3%, respectively). In AML patients, The median duration of neutropenia, was 8 days for imipenem/cilastatin and 12 days for cefepime, which was statistically significant ($p<0.02$).

The rate of success without modification was significantly higher in fever of unknown origin (FUO) episodes than (CDI) episodes (87.8% vs 12.2%).The differences between groups for both clinically and microbiologically defined infections were not statistically significant.

The rate of success without modification was significantly higher in HSCT recipients with thalassemia, MM, lymphoma and AA, than ALL, AML, CML and CLL ($P<0.001$).

Clinical response following antibiotic modification

Therapy modification was required in 32.4%, regardless of the initial treatment assigned (26.9% cefepime, 38% imipenem/cilastatin). Antibiotic modifications were similar between the treatment groups for all categories of infection (table 3).The most frequent modification of antibacterial study drug therapy consisted of the addition of a vancomycin, followed by addition of aminoglycoside (amikacin, 9% each treatment group). The addition of antifungal therapy did not differ between the imipenem/cilastatin (16 episodes, 32%) and the cefepime (10 episodes, 20%) groups.

Overall, the response rate of the multistep anti-infective strategy, with or without modification of the treatment assigned initially, was 100% in both treatment groups. No significant differences in success rate were observed between the treatment groups according to type of infection (Table 3).

Duration of Therapy, Fever, and Neutropenia

The difference between imipenem/cilastatin and cefepime was not statistically significant for duration of therapy and neutropenia, but was significant for duration of fever ($p<0.02$) and time of resolution of neutropenia ($p<0.018$). Because these data were not nor-

Table 3- Efficacy parameters of two regimens (Statistically differences define as asterisk)

	Imipenem/cilastatin		Cefepime		Total	
	n	(%)	n	(%)	N	(%)
Evaluable febrile episodes	52	(51)	50	(49)	102	(100)
Success without modification	38	(73.1)	31	(62)	69	(67.6)
FUO	24	(88.9)	19	(82.6)	43	(86)
Bacteremia	5	(83.3)	6	(66.7)	11	(73.3)
CDI	4	(36.4)	2	(20)	6	(28.6)
MDI	4	(80)	3	(60)	7	(70)
Bacteremia+MDI	1	(50)	1	(50)	2	(50)
Success with modification	14	(26.9)	19	(38)	33	(32.4)
FUO	3	(11.1)	4	(17.4)	7	(14)
Bacteremia	1	(16.7)	3	(33.3)	4	(26.7)
CDI	7	(63.3)	8	(80)	15	(71.4)
MDI	1	(20)	2	(40)	3	(30)
bacteremia+MDI	1	(50)	1	(50)	2	(50)
CDI+MDI	0		1	(100)	1	(100)
Bacteremia+CDI	1	(100)	0		1	(100)
Failure	0		0		0	
Source						
FUO	27	(51.9)	23	(46)	50	(49)
bacteremia	6	(11.5)	9	(18)	15	(14.7)
CDI	11	(21.2)	10	(20)	21	(20.6)
MDI	5	(9.6)	5	(10)	10	(9.8)
Bacteremia+MDI	2	(3.8)	2	(4)	4	(3.9)
CDI+MDI	0		1	(2)	1	(1)
Bacteremia+CD	1	(1.9)	0		1	(1)
Time of resolution of neutropenia(days)*	12		14		12	
Median time to defervescence (days)*	1.5		2		2	
Median duration of neutropenia(days)	9		12		10	
Median duration of antibiotic therapy(days)	7		7		7	
Vancomycin added	14	(26.9)	19	(38)	33	(32.4)

mally distributed, the re sults are appropriately described using the median and interquartile range. Median duration of treatment was 7 days in both groups. The median time to defervescence was 1.5 days (interquartile range, 1 to 6 days) for imipenem/cilastatin and 2 days (interquartile range, 1 to 8 days) for cefepime. The median time to resolution of neutropenia was 9 days (range, 4 to 24 days) for imipenem/cilastatin and 12 days (range, 3 to 27 days) for cefepime. The median time of resolution of neutropenia, after HSCT was 12 days (range, 7 to 25 days) for imipenem/cilastatin and 14 days (range, 8 to 38 days) for cefepime. In 65 episodes of success without modification, the median duration of neutropenia before entry was 4.9 days; whereas in 31 episodes where vancomycin was added, the median duration of ANC<500 before entry was 3.1 days (P<0.027).

Mortality

Death related to infection did not occur.

Toxicity

102 febrile events were evaluable for toxicity. Severe adverse events did not occuer. The overall rate of adverse effects considered related or probably related to study antibiotics was similar in the two treatment groups. In one episode cutaneous side effects with maculopapular rashes, probably related to imipenem/cilastatin were occurred. Mild to moderate nephrotoxicity probably attributable to the aminoglycoside developed in one episode in the cefepime group and two in the imipenem/cilastatin group. Hepatotoxicity and other intercurrent side effects were rarely associated with either of the antibiotic regimens. Diarrhea occurred in 7 febrile events treated with imipenem/cilastatin and in 8 of those with cefepime, but we did not judge the diarrhea to be definitively related to the study regimen because it may be due to GI mucositis or GVHD.

Discussion

Several studies have shown no striking differences between monotherapy and multidrug combinations for empirical treatment of un-

complicated episodes of fever in neutropenic patients [4,9,25-35]. A third- or fourth-generation cephalosporin (ceftazidime or cefepime) or a carbapenem (imipenem/cilastatin or meropenem) may be used successfully as monotherapy.[10] The patient must be monitored closely for nonresponse, emergence of secondary infections, adverse effects, and the development of drug-resistant organisms. Addition of other antibiotics may be necessary as the clinical course progresses. Cefepime, imipenem/cilastatin, and meropenem, unlike ceftazidime, have excellent activity against viridans streptococci and pneumococci.[13]

In patients with solid tumors the chemotherapy-induced neutropenia is usually of short duration and therefore characterized by a favorable outcome, but patients with leukemia or those treated by bone marrow transplantation are often predisposed to fatal complications.[2] Our RCT is the first studies that included only HSCT recipients with long duration of neutropenia. A median initial leukocyte count of 0.16×10^9/L and median duration of agranulocytosis of 10 days after study inclusion are further attributes characterizing our study as at substantial risk of severe complication.

Duration of ANC<500 after entry, leukocyte count at time of fever, mucositis occurrence and it's duration before entry, G-CSF and amphotericin B administration before and after entry, age, gender, type of conditioning regimens, graft type demonstrate no significant effect on response.

The overall response rates to initial monotherapy are dependent on the underlying disease, febrile episodes according to the kind of infection (FUO/bacteremia/CDI/MDI), duration of neutropenia before entry. However, the rate of successful clinical response was higher for Thalassemia, MM, AA and Lymphoma than for AML, ALL, CML and CLL, and in FUO episodes than CDI episodes, (Modification based on changing clinical parameters is necessary especially in cases of pneumonia and perianal infections for coverage of specific organism). The impact of duration of neutropenia before entry on response rate as shown in this study was higher in cases of successful response. After of neutropenia onset, the endogenous non pathogenic microflora (that are usually undetectable and present as FUO) need more time for invasion, than the potential pathogens or opportunistic pathogens with a virulent nature (that usually present as MDI or CDI) and FUO have more favorable outcome than other kinds of infection.

This investigation is the first to demonstrate a significant difference for imipenem/cilastatin over cefepime for 2 outcome measures, (the median time to defervescence and the median time to achievement neutrophil count over 500/μl). Furthermore, imipenem/cilastatin was also more effective than cefepime in subgroup of AML patients, treated with HSCT but the results must be interpreted with caution in the absence of data from a confirmatory trial in specific subsets of patients. The higher response rate for imipenem/cilastatin over cefepime may possibly reflect a broader spectrum of coverage against undetected unusual pathogens or resistant pathogens, but further investigation is required.

Single pathogen bacteremia occurred in 20.6% of our febrile episodes. That is in accordance with IATCG-EORTC studies VIII and IX with rate of 22% and lower than (XIV) trial with rate of 33%.[16,17,18,2,] Despite the extensive use of central venous catheters in our study population, this low rate may be due to poor detection of responsible pathogens in our blood sets. During the last 2 decades a shift to reverse gram negative (gr-) to gram positive (gr+) proportion has been observed.[1] Our findings showing proportion 43% gr- bacteremia is in accordance with this evolution. CoNS were the most common isolates from gr+ bacteremia (71%, remaining s. aureus). CoNS bacteremia is frequently related to the use of central venous catheters, as CoNS are predominant members of the skin microflora. However, CoNS are also present in the endogenous flora of the mucosa of mouth and gastrointestinal tract of neutropenic patients. Plasmid pattern analysis on CoNS bloodstream isolates revealed that the mucosa was the origin in 70% of hematologic patients.[19, 20, 24] Escherichia coli were the most common causes of Gram-negative bacillary bacteremia (87.5%), remaining Acinetobacter. Unusual but more resistant pathogens, such as Acinetobacter species, Stenotrophomonas maltophilia and Capnocytophaga species are occasionally isolated and are related to either gastrointestinal or oral mucositis.[19] The types of

pathogens isolated from patients in our trial were consistent with those commonly associated with infection in neutropenic patients.[5]

Our overall response rate (success without modification) of 68% is compatible to IATCG-EORTC VIII and IX studies and recent trials.[25,14,16,17] Because definitions of response are not consistent among published trials, it is difficult to directly compare results from this trial with other trials testing the value of empirical antibiotic therapy for febrile neutropenia. Moreover, outcome in neutropenia trials may be affected by the response definitions used when the major end point compares the response rate of two or more initial antibiotic regimens. In term of MDI and CDI our results (20.6%, 14.7%) are compatible to IATCG-EORTC VIII and IX studies and recent trials [16,17,2].

Vancomycin was added following the defined criteria in 33 % of the episodes. This is in keeping with result of recent studies [2,16]. Because the spectrum of drugs used for monotherapy does not usually cover coagulase-negative staphylococci, methicillin-resistant S. aureus, enterococci, some strains of penicillin-resistant Streptococcus pneumoniae, and viridans streptococci, we included vancomycin as second line in empiric regimens. Inclusion of vancomycin in initial empirical therapy may be prudent for selected patients with the specific clinical findings (36). After modification, the success rate was 100% in both treatment groups which is accordance to recent trials with rate of 95-100%.[29,23]

Considering study in HSCT recipients, no systemic invasive mycosis was observed, due to no dust enviroment by cleaning all surfaces, isolating patient care wards from outside air, maintaining negative pressure in construction areas and providing patients with masks when moving into unprotected areas, installing HEPA filtration in ventilation system. Pre-emptive antifungal therapy: initiating antifungal agents in persistently febrile neutropenic patients who have a probable IFI on the basis of significant colonization, positive serology, clinical, or radiological findings. Empirical antifungal therapy: provides antifungal agents to neutropenic patients who have persistent fever despite broad-spectrum antibiotics but do not exhibit the clinical or laboratory findings suggestive of IFI (mentioned above).Antifungal prophylaxis: provides antifungal agents before any evidence of fungal colonization or infection; it is usually given at initiation of immunosuppression.

As expected, the observed toxicity was low in both arms, leading to discountinuation of treatment in only 1 patient.

In conclusion, our results demonstrate that imipenem/cilastatin and cefepime are effective and well tolerated when used as initial empirical treatment for HSCT recipient with prolonged neutropenia. Imipenem/cilastatin may be more effective than cefepime, as evidenced by a significantly better response in two outcome measures. Although imipenem/cilastatin were also more effective than cefepime in one subgroup of patients (AML), the results must be interpreted with caution in the absence of data from a confirmatory trial in the specific subsets of patients.

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