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Results of a Multicenter, Controlled, Randomized Clinical Trial Evaluating the Combination of Piperacillin/Tazobactam and Tigecycline in High-Risk Hematologic Patients With Cancer With Febrile Neutropenia

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
Empiric antibiotic monotherapy is considered the standard of treatment for febrile neutropenic patients with cancer, but this approach may be inadequate because of the increasing prevalence of infections caused by multidrug resistant (MDR) bacteria.

Patients and Methods
In this multicenter, open-label, randomized, superiority trial, adult, febrile, high-risk neutropenic patients (FhrNPs) with hematologic malignancies were randomly assigned to receive piperacillin/tazobactam (4.5 g intravenously every 8 hours) with or without tigecycline (50 mg intravenously every 12 hours; loading dose 100 mg). The primary end point was resolution of febrile episode without modifications of the initial allocated treatment.

Results
Three hundred ninety FhrNPs were enrolled (combination/monotherapy, 187/203) and were included in the intention-to-treat analysis (ITTA). The ITTA revealed a successful outcome in 67.9% *v* 44.3% of patients who had received combination therapy and monotherapy, respectively (127/187 *v* 90/203; absolute difference in risk (adr), 23.6%; 95% CI, 14% to 33%; $P < .001$). The combination regimen proved better than monotherapy in bacteremias (adr, 32.8%; 95% CI, 19% to 46%; $P < .001$) and in clinically documented infections (adr, 36%; 95% CI, 9% to 64%; $P < .01$). Mortality and number of adverse effects were limited and similar in the two groups.

Conclusion
The combination of piperacillin/tazobactam and tigecycline is safe, well tolerated, and more effective than piperacillin/tazobactam alone in febrile, high-risk, neutropenic hematologic patients with cancer. In epidemiologic settings characterized by a high prevalence of infections because of MDR microorganisms, this combination could be considered as one of the first-line empiric antibiotic therapies.

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INTRODUCTION

Patients with cancer who become granulocytopenic as a result of intensive myelosuppressive chemotherapy are at high risk of developing infections,[1] which may be lethal if empiric antibiotic treatment is not promptly instituted. Nowadays, single-agent empiric antibacterial therapy may be considered the standard of treatment.[1-3] Over the past 30 years, there has been a continuous change in the epidemiology of bacterial infections in neutropenic patients with cancer. Although Gram-positive cocci still represent the source of over 60% of bacteremias,[4-6] a new emergence of gram negatives has occurred, and the diffusion of multidrug resistant (MDR) microorganisms has been observed.[6-11] These new epidemiologic settings in neutropenic patients with cancer may be responsible for the inadequacy of the commonly used empiric monotherapy regimens,[12,13] which has led to an increased mortality.[14,15] New anti-Gram-positive drugs are currently available, but there are only a few therapeutic options for MDR Gram-negative infections. Tigecycline, the first in a new class of glycylcyclines, is characterized by a broad

antibacterial spectrum that covers the majority of MDR Gram-positive and Gram-negative strains, with the exclusion of *Pseudomonas aeruginosa* and Proteeae.[16-21] Few clinical data on the safety and effectiveness of tigecycline in neutropenic patients with cancer are available.[22] To investigate the possible benefits resulting from the combination of this drug with the currently used monotherapy regimens, we have conducted a large, controlled randomized clinical trial by using piperacillin/tazobactam with or without tigecycline as empirical antibiotic therapy in febrile neutropenic adult patients with hematologic malignancies.

PATIENTS AND METHODS

Study Design and Participants

The study was a prospective, multicenter, unblinded, randomized, controlled, superiority trial planned, conducted, and analyzed by the Gruppo Italiano Malattie Ematologiche dell'Adulto Infection Program. It was registered in the EU Clinical Trials Database and approved by the ethics committee at each participating center. The study was conducted between May 3, 2008, and November 4, 2010, at 28 centers in Italy. Written informed consent was obtained from each patient.

Consecutive adult patients with hematologic malignancies undergoing intensive chemotherapy or conditioning regimens for autologous hematopoietic stem-cell transplantation were eligible to be randomly assigned if they had fever ($\geq$ 38.5°C on one occasion or $\geq$ 38°C on two or more occasions within 12 hours), chemotherapy-induced neutropenia (absolute neutrophils count $<$ 1,000 per cubic millimeter anticipated to decrease to fewer than 500 cells per cubic millimeter within 24 to 48 hours), and a presumed infection (ie, fever not likely to be due to a noninfectious cause such as drug or blood product administration). Patients were enrolled only once in the study. Patients were excluded if they had received any intravenous antibiotics during the preceding 96 hours. Additional exclusion criteria are provided in the Appendix (online only). Quinolones prophylaxis was discontinued at randomization.

Trial Objectives

The primary objective of the study was to show superiority in the rates of successful response (defined as resolution of fever and clinical signs of infection and eradication of the infecting microorganisms, without modifications of the initial allocated treatment) of the combination over the monotherapy regimen. A response was defined as a failure if the patient died as a result of the primary infection; if bacteremia persisted beyond the first 24 hours of therapy; if a breakthrough bacteremia occurred; if the isolated pathogen was resistant to the assigned antibiotics; if no response was seen after at least 72 hours of therapy; if shock or acute respiratory distress syndrome or disseminated intravascular coagulation or multiple organ failure was observed; if infection relapsed within 7 days of treatment discontinuation; and if a toxicity attributed to protocol antibiotics that required the interruption of treatment occurred. Secondary end points were safety and tolerability. Survival at day 30 was also evaluated.

Clinical and Microbiologic Assessment, Follow-Up

Details on baseline and follow-up assessments are provided in the Appendix. Patients were evaluated for response at day 4 after empirical therapy initiation (early evaluation) and at the completion of the trial (overall evaluation). Standardized efforts to evaluate persistent or relapsing fever were made. Infections were classified according to the definitions of the European Organization for Research and Treatment of Cancer.[23]

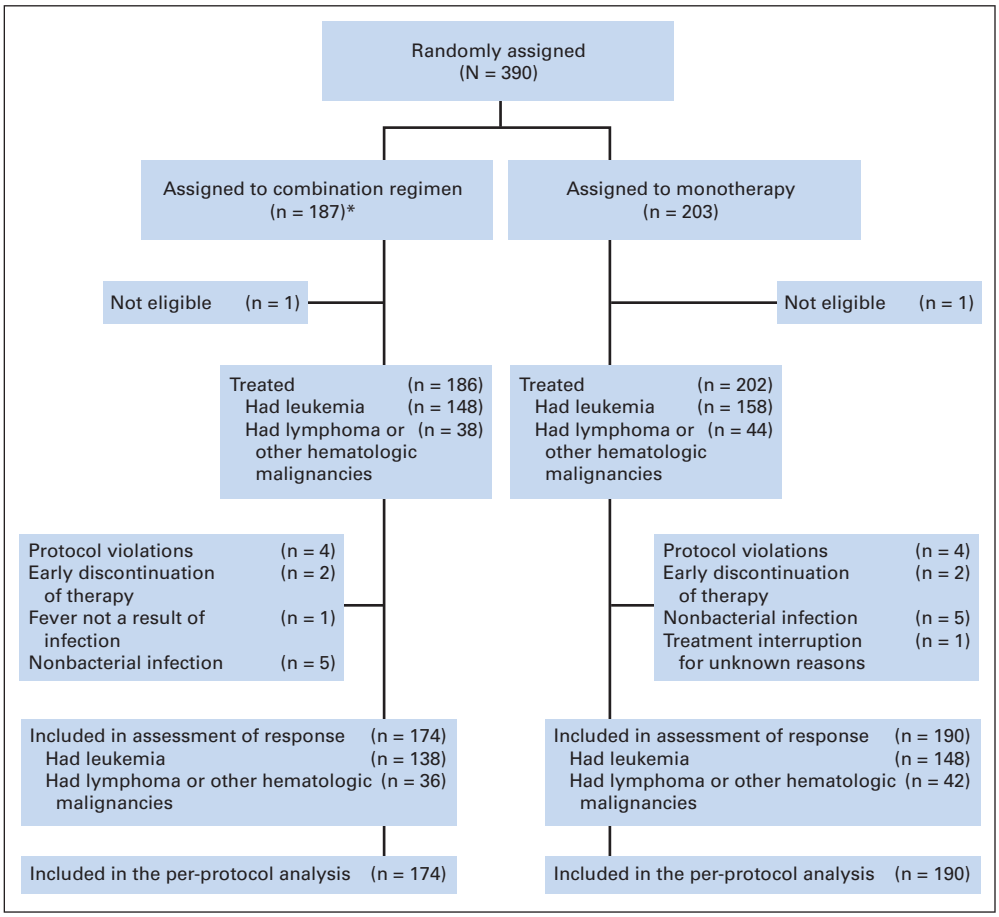

Fig 1. Enrollment and outcome. (*) The trial enrollment was stopped shortly before reaching the planned number (190) in this arm of the study because of impending expiry of the study insurance contract. However, after having consulted the central ethical committee, considering the large and conservative anticipated rate of not evaluability assumed in the sample size calculation, the data review committee was confident that an adequate number of evaluable patients would have been reached in each group of treatment, as it actually occurred.

Isolates identification and their susceptibility to antibiotics were evaluated at each participating center according to the Clinical and Laboratory Standards Institute guidelines.[24] The growth of coagulase-negative staphylococci (CNS) was considered as bacteremia when two or more blood cultures, drawn in separate occasions within 24 hours, yielded the same microorganism. Extended spectrum beta-lactamase production in Enterobacteriaceae was routinely carried out in three large centers. The minimum inhibitory concentration (MIC) for tigecycline was determined by using Etest (AB-BioMérieux, Solna, Sweden), and the MIC breakpoints for susceptibility issued by the European Committee on Antimicrobial Susceptibility Testing ($\leq$ 1 mg/L) were used.[25]

Study Drug Treatment

At the onset of fever, patients were randomly assigned to receive piperacillin/tazobactam (4.5 g intravenously every 8 hours) with or without tigecycline (50 mg intravenously every 12 hours, loading dose of 100 mg) as empiric therapy. Antibiotic treatment was continued until success or failure was decided. The assigned therapy could be modified before day 4 only in the case of a worsening of the patient's clinical condition or if the isolated pathogen was resistant to the assigned antibiotics, otherwise the modification was considered a protocol violation.

Randomization and Statistical Analysis

Patients were centrally randomly assigned by using an automated computer randomization procedure. The randomization list was created by using a computer random generator program (Epistat, version 2) and was stratified by center and underlying disease with a 1:1 allocation by using a block size of eight. Participating centers were not aware of block size (Appendix).

According to our previous study,[12] we assumed that a favorable response would occur in approximately 50% of patients empirically treated with a piperacillin/tazobactam monotherapy regimen. We estimated that at least 340 patients (170 in each group) would be needed to detect an absolute difference of at least 15% between monotherapy and the combination regimen, with a statistical power of 80% and a 5% significance level. Anticipating a 10% nonevaluability rate, we planned to include at least 380 patients (190 in each group) in the trial.

All case report forms were centrally reviewed by the data review committee and entered into the computer system blinded for the assigned regimen. Statistical analyses were carried out at the Gruppo Italiano Malattie Ematologiche dell'Adulto Infection Program Data Center with the use of the SPSS software package (SPSS, Chicago, IL) and were made in a blinded fashion with respect to the assigned treatment. An analysis that included all eligible patients was deemed according to the intention to treat by considering that treatment was considered as failed in patients in whom response could not be assessed because they were lost to follow-up. A per-protocol analysis that included all assessable patients was conducted. Efficacy with respect to the primary and secondary end points was expressed as the absolute difference in rates between treatment groups (combination minus monotherapy regimen). The 95% CI for the difference between proportions was given. The χ^2 test with a correction for continuity or Fisher's exact test for small samples when necessary was used to compare proportions. The Wilcoxon rank sum test was used to compare continuous variables. A backward stepwise logistic regression model was used to assess the relative importance of the various prognostic factors assessable at the time of randomization.

Table 1. Demographics and Clinical Characteristics of the 390 Patients Who Entered Onto the Study

Characteristic	Pip/Tazo + Tigecycline No.	Pip/Tazo + Tigecycline %	Pip/Tazo No.	Pip/Tazo %
Patients	187		203	
Sex				
Male	104		102	
Female	83		101	
Age				
Mean	54		53	
Range	18-76		21-76	
Underlying cancer				
Acute leukemia	146	78	158	77.8
Lymphoma	30	16	28	13.8
Other hematologic malignancies	11	6	17	8.4
Chemotherapy				
Remission induction/reinduction	110	58.8	117	57.6
Remission consolidation	36	19.2	41	20.2
Autologous stem-cell transplantation	28	15	36	17.7
Other	13	7	9	4.5
Use of growth factors	30	16	34	16.7
Oral antibacterial prophylaxis before randomization	175	93.6	194	95.6
Antifungal prophylaxis	140	74.9	170	83.7
Antiviral prophylaxis	64	34.2	79	38.9
Intravenous catheter in situ	133	71.1	147	72.4
Protective environment*	119	63.6	131	64.5
Single room	62		69	
Reverse isolation	2		2	
Laminar air flow room	37		43	
Other	18		17	
Duration of granulocytopenia, days (neutrophils/mL)				
< 1,000				
Mean	22		20	
Range	1-142		1-61	
Median	18		17	
< 500				
Mean	11		12	
Range	1-50		1-61	
Median	10		10	
Neutrophil count at entry (< 100 neutrophils/mL)	159	85	174	85.7

Abbreviation: Pip/Tazo, piperacillin/tazobactam.
*Specific infection control measures for the prevention of carbapenem-resistant strains spread were not routinely instituted.

RESULTS

A total of 390 febrile neutropenic hematologic patients with cancer were enrolled: 187 assigned to receive intravenous piperacillin/tazobactam plus tigecycline; 203 intravenous piperacillin/tazobactam. The enrolment and outcome are shown in Figure 1. The characteristics of patients included onto the study are provided in Table 1.

Response to Therapy

The rates and the absolute differences in the risk (adr) of primary and secondary end points are shown in Figure 2. An intention-to-treat analysis performed on the 390 eligible patients revealed that a successful outcome was obtained in 67.9% of patients in the combination group, compared with 44.3% of patients in the monotherapy group ($P < .001$).

A per-protocol analysis of patients whose response to the assigned treatment could be assessed yielded similar results. The response rate of microbiologically documented infections was significantly higher in the combination group than in the monotherapy treated patients (61.4% *v* 28.1%; $P = .001$).

Overall, 97.8% (180 of 184) of the microbiologically documented infections were bacteremias (Fig 2). The distribution of bacteremias, as well as the type of isolated pathogens, was similar in both treatment groups, with CNS and *Escherichia coli* being the most frequent isolates.

Group and Event	Combination No.	Combination %	Monotherapy No.	Monotherapy %	Absolute Difference in Risk	95% CI
All treated patients						
Febrile episode resolution	127 of 187	67.9	90 of 203	44.3	0.23	0.14 to 0.33
Death	16 of 187	8.5	15 of 203	7.3	0.01	-0.04 to 0.06
Death resulting from infective cause	11 of 187	5.8	11 of 203	5.4	0.004	-0.04 to 0.05
AEs	12 of 187	6.4	13 of 203	6.4	0.0001	-0.04 to 0.04
Withdrawal due to AEs	3 of 187	1.6	5 of 203	2.4	-0.008	-0.03 to 0.01
All assessable patients						
Febrile episode resolution	126 of 174	72.4	90 of 190	47.4	0.25	0.15 to 0.34
Microbiologically documented infections	54 of 88	61.4	27 of 96	28.1	0.33	0.19 to 0.46
Bacteremia	52 of 86	60.5	26 of 94	27.7	0.32	0.19 to 0.46
Gram positive	30 of 42	71.4	16 of 46	34.8	0.36	0.17 to 0.56
Staphylococcus aureus			2 of 4	50.0		
*Coagulase-negative Staph**	20 of 26	76.9	9 of 29	31.0	0.45	0.22 to 0.69
Enterococci	2 of 3	66.7	3 of 6	50.0	0.16	-0.50 to 0.83
Streptoocci	5 of 7	71.4	2 of 5	40.0	0.31	-0.23 to 0.85
Other gram positive	3 of 6	50.0	0 of 2	0.0	0.50	0.09 to 0.90
Gram negative	18 of 34	52.9	7 of 29	24.1	0.28	0.05 to 0.51
Escherichia coli	15 of 22	68.2	4 of 17	23.5	0.44	0.16 to 0.72
Pseudomonas spp	0 of 5	0.0	1 of 5	20.0	-0.20	-0.55 to 0.15
Klebsiella spp	2 of 4	50.0	0 of 3	0.0	0.50	0.01 to 0.99
Other gram negative	1 of 3	33.3	2 of 4	50.0	-0.16	-0.89 to 0.55
Polymicrobial	4 of 10	40.0	3 of 19	15.8	0.24	-0.10 to 0.58
Clinically documented infection	16 of 19	84.2	9 of 19	47.4	0.36	0.09 to 0.64
Fever of unknown origin	56 of 67	83.6	54 of 75	72.0	0.11	-0.01 to 0.25
Documented infections	70 of 107	65.4	36 of 115	31.3	0.34	0.21 to 0.46
Pneumonia	5 of 7	71.4	4 of 8	50.0	0.21	-0.26 to 0.69
Central venous catheter	5 of 8	62.5	6 of 17	35.3	0.27	-0.13 to 0.67
Abdominal	4 of 8	50.0	1 of 6	16.7	0.33	-0.12 to 0.79
SSTI†	6 of 6	100	1 of 7	14.3	0.85	0.59 to 1.12

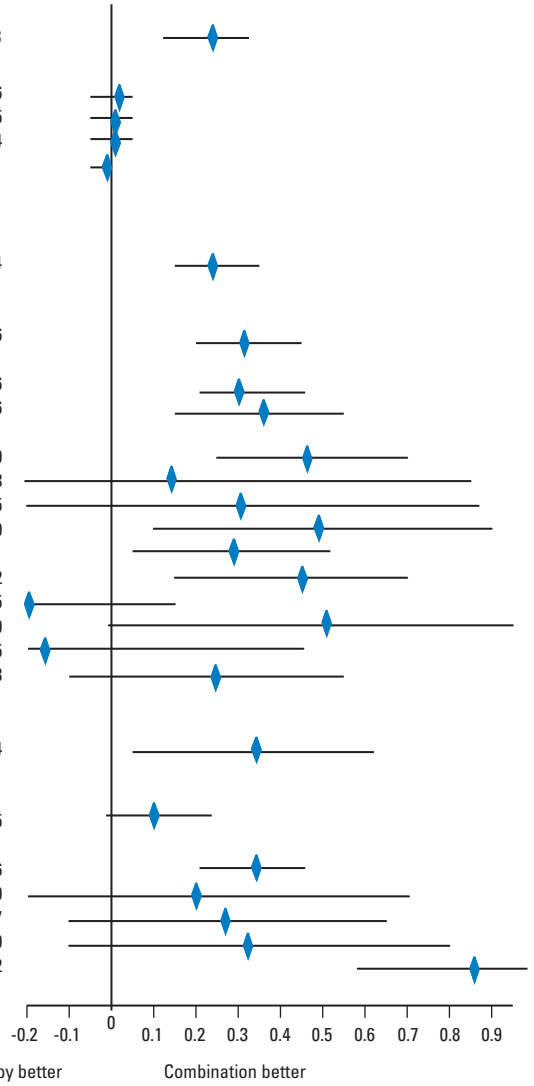

Fig 2. Rates and absolute differences in the risk of primary and secondary end points. (*) Overall, data on methicillin-resistance (MR) were available for 44 of 55 strains (80%); 35 of 44 (79.5%) coagulase-negative *Staphylococcus* were MR. (†) Severe skin and soft tissue infection (SSTI). AE, adverse event.

CNS blood isolates were methicillin-resistant in 79.5% of cases. The prevalence of ESBL-producing strains documented by the three centers that routinely performed the screening and considered as representative sample accounted for 30% of Enterobacteriaceae.

The success rate of patients with bacteremia treated with the combination was 60.5%, compared with 27.7% of those treated with monotherapy ($P < .001$). Significantly higher success rates were observed in patients with CNS and *E coli* bacteremia (Fig 2).

The reasons for failure are shown in Table 2. Failure because of an isolate resistant to the initial allocated regimen occurred in eight of 174 patients treated with combination therapy (4.6%) compared with 27 of 190 patients treated with monotherapy (14.2%) (adr, −0.09; 95% CI, −0.15 to −0.03; $P = .001$). Susceptibilities of single agents and polymicrobial bacteremias isolates are shown in Table 3. Resistant pathogens were equally distributed in the two treatment groups. No differences were detected in the number of days to defervescence that were two (median, range 1 to 10) and three (median, range 1 to 17) in patients treated with combination therapy and monotherapy, respectively. The time to failure values were similar in both groups with a median number of days to failure of 4 (range, 1 to 13 for combination therapy and 1 to 17 for monotherapy).

Modification of the Allocated Antibiotic Regimen

Data on antibiotics prescribed as second-line treatment were available for 91% of cases of failure. A carbapenem (alone or in combination) replaced the first-line regimen in 72.8% (99 of 136) of failed cases, but overall 27.1% (99 of 364) of the assessable population received a carbapenem. The use of an antipseudomonal cephalosporin or a

Table 2. Reasons for Failure

Reasons for Failure	Pip/Tazo + Tigecycline, 174 Assessable Patients Total Failures (n = 48) No.	%	Pip/Tazo, 190 Assessable Patients Total Failures (n = 100) No.	%
Subjective	21	43.8	41	41
Persistent fever or relapsing fever	15	31.3	29	29
Progression of primary infection	6	12.5	12	12
Objective	27	56.2	59	59
Persistent bacteremia	6	12.5	10	10
Resistant pathogen	5	10.4	17	17
Breakthrough bacteremia	3	6.2	9	9
Shock, ARDS, multiorgan failure	2	4.3	4	4
Withdrawal because of toxicity	3	6.2	5	5
Death as a result of the primary infection	3	6.2	1	1
Two or more reasons	5	10.4	13	13

Abbreviations: ARDS, acute respiratory distress syndrome; Pip/Tazo, piperacillin/tazobactam.

carbapenem was significantly higher in the monotherapy than in the combination regimen (67 of 183, 36.6% *v* 37 of 169, 21.9%; adr, 0.14; 95% CI, 0.05 to 0.24; $P < .01$). Similarly an anti-Gram-positive agent was used as second-line treatment in 69 of 183 (37.7%) and 25 of 169 (14.8%) of cases, respectively, in the monotherapy and in the combination regimen (adr, 0.23; 95% CI, 0.14 to 0.31; $P < .01$).

Tigecycline was used as second-line therapy in 34 of 100 patients who failed on piperacillin/tazobactam monotherapy. In the 26 assessable cases, the success rate was 69% in 16 bacteremias and in three clinically documented infections, and it was 86% in seven cases of unexplained fever.

Multivariable Analysis

To estimate predictive factors that could influence the failure of empiric therapy, data from all assessable patients were fitted within a multivariable logistic regression model. Factors included in the model were as follows: antibiotic regimen, sex, age, performance status (WHO five-degree scale), underlying disease, neutrophil count at onset of fever, and duration of neutropenia. Although the duration of neutropenia $\geq$ 10 days, acute leukemia, and monotherapy were significant factors for failure at the univariable level, only the last two resulted independent risk factors at the multivariable level (Table 4).

Mortality

The mortality rates and causes of death were equally distributed between the two treatment groups (Table 5). Overall, 16 patients (8.5%) who were in the combination group died, compared with 15 (7.3%) in the monotherapy group ($P = .4$). Eleven patients died as a result of infectious causes in both treatment groups. Overall, 16 deaths were bacteremia related, and in 11 cases (68.7%) a Gram-negative microorganism was involved.

The bacteremia-related mortality rates were similar, being 4% in both regimens ($P = .4$). Early death (within 72 hours from the start of the empiric therapy) in bacteremic febrile episodes occurred in one of 187 patients (0.5%) treated with combination regimen and in four of 203 patients (2%) treated with monotherapy ($P = .2$; estimated relative risk, 0.27; 95% CI, 0.03 to 2.41), and a Gram-negative strain was involved in four of five cases.

Adverse Events

Three hundred ninety patients were assessable for adverse events. The overall incidence of adverse events was 6.4% in both treatment groups (12 of 187 in the combination and 13 of 203 in the monotherapy group). Nausea, vomiting, and diarrhea occurred in seven patients (3.7%) treated with tigecycline. Toxicities resulted in the discontinuation of treatment in three patients undergoing the combination and in five receiving monotherapy.

Table 3. Pip/Tazo, Tigecycline, and Levofloxacin Resistance in Single-Agent and Polymicrobial Bacteremias

Organism	Pip/Tazo No. Resistant/Total No. Available for Analysis	%	Tigecyclin No. Resistant/Total No. Available for Analysis	%	Levofloxacin No. Resistant/Total No. Available for Analysis	%
Escherichia coli	15/46	33	3/44	7	39/40	97
Pseudomonas spp	5/9	55	9/9	100	7/8	87
Klebsiella spp	4/11	36	1/10	10	10/10	100
Other Gram negative	2/5	40	0/3	0	2/4	50
Total gram-negative organisms	26/71	37	13/66	20	58/62	94
Staphylococcus aureus	3/7	43	1/7	14	2/6	33
MRSA	3/3	100	1/3	33	2/2	100
MSSA	0/4	0	0/4	0	0/4	0
Coagulase-negative *Staphylococcus*	58/62	94	4/58	7	51/61	84
MRCNS	53/53	100	3/43	7	37/45	82
MSCNS	5/9	55	1/15	7	14/16	87
Enterococcus spp	7/11	64	2/11	18	6/9	67
Streptococcus spp	1/10	10	0/8	0	10/12	83
Other Gram positive	2/4	50	2/5	40	3/3	100
Total gram-positive organisms	71/94	75	9/89	10	72/91	79

Abbreviations: MRCNS, methicillin-resistant coagulase-negative *Staphylococcus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSCNS, methicillin-susceptible coaulase-negative *Staphylococcus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; pip/tazo, piperacillin/tazobactam.

Table 4. Multivariable Backward, Logistic Regression Model: Factors Associated With the Failure of Empiric Antibiotic Therapy

Variables	Category	OR	95% CI	*P*
Antibiotic regimen	Monotherapy	2.86	1.59 to 4.12	< .001
	Combination	1		
Underlying disease	Acute leukemia	2.54	1.18 to 3.90	.002
	Other hematologic malignancies	1		

NOTE. Others factors included in the model but not associated with the failure of empiric antibiotic therapy were as follows: Sex: male *v* female; age (years): ≤ 65 *v* > 65; performance status (WHO five points scale) ≤ 2 *v* > 2; neutrophil count at onset of fever: ≤ 100/mL *v* > 100/mL; and duration of neutropenia (days): < 10 *v* ≥ 10.
Abbreviation: OR, odds ratio.

DISCUSSION

The increase of relative proportion of bacteremias caused by gram negatives[6-8] and, at the same time the emergence of MDR microorganisms,[9-11] may be responsible for the inadequacy of monotherapy regimens, as well as of the classical β-lactam and aminoglycoside combination for the empiric treatment of febrile neutropenia in patients with cancer.[2,11-13] In this context, our study addresses two important issues: whether an association of antibiotics is better than monotherapy and whether tigecycline in combination can be used as empiric antibiotic therapy.

To our knowledge, this is the first multicenter, randomized, controlled, prospective trial powered to demonstrate that the combination of piperacillin/tazobactam with tigecycline is more effective than piperacillin/tazobactam alone for the empiric treatment of fever in persistently granulocytopenic patients with cancer. Combination regimen was associated with a significantly higher success rate compared with monotherapy in patients with bacteremia, as well as in patients with clinically documented infections. The use of the same antipseudomonal drug in the two arms of treatment and the uniform protocol guidelines for therapeutic decisions enabled us to attribute the differences in clinical responses exclusively to tigecycline.

Our study was open label. Unfortunately, the high cost of double dummy preparations and the difficulties to guarantee the use of an adequate masking technique in each participating center (because of the easily recognizable orange color of tigecycline solution), made the blinded design unaffordable for a spontaneous no-profit study.

Our methodology was aimed at reducing the possibility of bias in the interpretation of the results. Moreover, all the data recorded in the case report forms were entered into the computer system and assessed blinded for the assigned regimen by the data review committee.

In any case, the investigators' judgment does not seem to have been influenced by the unblinded design. In our study, both persistent or relapsing fever and progression of infection were considered and analyzed as reasons for failure burdened by subjectivity compared with other more objective and verifiable reasons. As shown in Table 3,

Table 5. Mortality Rates in the Treated Population

Variable	Pip/Tazo + Tigecycline (N = 187)		Pip/Tazo (N = 203)		Absolute Difference in Risk (95% CI)	
	No.	%	No.	%		*P*
Death	16	8.5	15	7.3	0.01 (−0.04 to 0.06)	0.4
Death because of infection	11	5.8	11	5.4	0.004 (−0.04 to 0.05)	0.5
Microbiologically documented infection with bacteremia	8	4.2	8	3.9	0.003 (−0.03 to 0.04)	0.4
Single gram-negative isolate	5	2.7	3	1.5		
Escherichia coli	2		2			
Klebsiella spp	1		—			
Pseudomonas spp	2		1			
Single gram-positive isolate	2	1	2	1		
Enterococcus spp	1		1			
Streptococcus spp	1		—			
Methicillin-resistant coagulase-negative *Staphylococcus*	—		1			
Polymicrobial	1	0.5	3	1.4		
E coli plus gram-positive organism	1		2			
Gram-positive organisms only	—		1			
Clinically documented infection	1	0.5	1	0.5		
Fever of unexplained origin	—		1			
Death because of fungal infection	2	1	1	0.5		
Death from noninfectious causes*	5	2.7	4	1.9	0.007 (−0.02 to 0.03)	0.4
Bacteremia-related early death (death occurring within 72 hours from the start of empiric therapy)	1	0.5	4	2	−0.01 (−0.03 to 0.007)	0.2
Single agent bacteremia†	1		3			
Polymicrobial bacteremia	0		1‡			

Abbreviation: pip/tazo, piperacillin/tazobactam.
*Deaths occurred within the 7-day period after antibiotic treatment (including modification of the assigned regimen) discontinuation.
†Combination therapy: one *E coli*; Monotherapy: two *E coli* and one coagulase-negative *Staphylococcus*.
‡*E coli* plus *Enterococcus spp*.

each reason for failure was equally distributed between the two treatment groups, and an objective and verifiable reason for failure represented approximately 60% of the total causes of failure in both treatment arms. Noteworthy, even if all the cases that failed because of a possible investigator's subjective judgment were reclassified as successes, the success rate of the combination was still higher than that of monotherapy (147 of 174 *v* 131 of 190; adr, 15%; 95% CI, 7% to 24%; $P < .001$).

Tigecycline in combination with an antipseudomonal agent was effective regardless of the site of the infection. A substantial better response of the combination regimen was documented in bacteremias, in particular those caused by staphylococci and *E coli*. Because tigecycline achieves modest plasma concentrations, concerns were raised about its efficacy in the treatment of bacteremias and infections with organisms with a higher MIC.[26-30] However, no studies have been designed to evaluate the efficacy of tigecycline in bacteremias, although Chemaly[22] observed a good clinical response by using tigecycline for refractory bacteremias in patients with cancer.

In our study, the results of the combination regimen in bacteremias might have been influenced by an overall better in vitro activity of tigecycline against blood isolates compared with that of piperacillin/tazobactam and also by the low incidence of bacteremias because of *P aeruginosa*, not covered by the tigecycline spectrum of activity. Noteworthy, in the combination arm, more than 30% of pathogens involved in single agent bacteremias were susceptible only to tigecycline, whereas tigecycline was the only active drug against the involved microorganisms in 60% of polymicrobial bacteremias. In patients with cancer, the reported rates of ESBL producer among *E coli* causing bacteremias account for up to 40%.[14,15,31,32] At the same time, mortality and the delay of effective therapy have been associated with ESBL production in Enterobacteriaceae bacteremia.[15,31,32] The results of our study seems to indicate that in febrile, high-risk neutropenic patients (FhrNPs) the addition of tigecycline, active also against ESBL producers, could improve the adequacy of initial empiric monotherapy, and they also suggest that tigecycline in combination may contribute to reduce the overuse of carbapenems (overall, in our study, only the 27% of assessable population received a carbapenem) and anti-Gram-positive agents, as strongly recommended for the prevention of emergence of resistance.[33,34]

This study was not powered to document an effect of the tigecycline combination in the reduction of mortality that in neutropenic patients with cancer may be also influenced by factors other than the empiric antibiotic therapy. The overall mortality rate evaluated at the end of the febrile episode was limited and similar in the two treatment groups. However, in patients receiving the combination therapy, we observed that a lower number of bacteremia-related early deaths occurred under the assigned antibiotic regimen (a Gram-negative was involved in four of five cases). Even if the difference was not statistically significant, it should be noted that in the combination arm only 12% of deaths because of bacteremia occurred within the first 72 hours from the start of empiric antibiotic therapy, compared with 50% in the monotherapy arm. This result is in line with studies revealing a better outcome and a higher overall survival rate in patients receiving initial adequate antibiotic therapy.[10,14,31,32] The study confirms that in FhrNPs, tigecycline is safe and well tolerated.

In conclusion, the results of our study support the view[35] that a broad initial empirical combination regimen should be reserved to FhrNPs at high risk of developing infections because of MDR pathogens.

Because the majority of our patients was affected by acute leukemia, which was an independent factor for antibiotic treatment failure, and they had received intensive chemotherapy, the results of our study may not pertain to patients affected by other types of cancer, undergoing less intensive chemotherapy, and not receiving quinolones prophylaxis. We therefore believe that the combination containing tigecycline should be used as empiric therapy only for febrile neutropenic patients with acute leukemia in epidemiologic settings characterized by a high rate of MDR microorganisms, such as those observed in our study. The knowledge of local epidemiology is needed to drive the empiric antibiotic strategies together with a stringent enforcement of antibiotic stewardship programs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Hughes WT, Armstrong D, Bodey GP, et al: From the Infectious Diseases Society of America. Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. J Infect Dis 161:381-396, 1990

2. Freifeld AG, Bow EJ, Sepkowitz KA, et al: Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 52:56-93, 2011

3. Meunier F, Lukan C: The First European Conference on Infections in Leukaemia–ECIL1: A current perspective. Eur J Cancer 44:2112-2117, 2008

4. Viscoli C, Varnier O, Marchetti M: Infections in patients with febrile neutropenia: Epidemiology, microbiology, and risk stratification. Clin Infect Dis 40:S240-S245, 2005

5. Wisplinghoff H, Seifert H, Wenzel RP, et al: Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. Clin Infect Dis 36:1103-1110, 2003

6. Klastersky J, Ameye L, Maertens J, et al: Bacteraemia in febrile neutropenic cancer patients. Int J Antimicrob Agents 30:S51-S59, 2007 (suppl 1)

7. Bucaneve G, Micozzi A, Menichetti F, et al: Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med 353:977-987, 2005

8. Mikulska M, Del Bono V, Raiola AM, et al: Blood stream infections in allogeneic hematopoietic stem cell transplant recipients: Reemergence of Gram-negative rods and increasing antibiotic resistance. Biol Blood Marrow Transplant 15:47-53, 2009

9. Cattaneo C, Quaresmini G, Casari S, et al: Recent changes in bacterial epidemiology and the emergence of fluoroquinolone-resistant Escherichia coli among patients with haematological malignancies: Results of a prospective study on 823 patients at a single institution. J Antimicrob Chemother 61:721-728, 2008

10. Gudiol C, Calatayud L, Garcia-Vidal C, et al: Bacteraemia due to extended-spectrum beta-lactamase-producing Escherichia coli (ESBL-EC) in cancer patients: Clinical features, risk factors, molecular epidemiology and outcome. J Antimicrob Chemother 65:333-341, 2010

11. Trecarichi EM, Tumbarello M, Spanu T, et al: Incidence and clinical impact of extended-spectrum-beta-lactamase (ESBL) production and fluoroquinolone resistance in bloodstream infections caused by Escherichia coli in patients with hematological malignancies. J Infect 58:299-307, 2009

12. Del Favero A, Menichetti F, Martino P, et al: A multicenter, double-blind, placebo-controlled trial comparing piperacillin-tazobactam with and without amikacin as empiric therapy for febrile neutropenia. Clin Infect Dis 33:1295-1301, 2001

13. Cometta A, Calandra T, Gaya H, et al: Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. 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. Antimicrob Agents Chemother 40:1108-1115, 1996

14. Tumbarello M, Sanguinetti M, Montuori E, et al: Predictors of mortality in patients with bloodstream infections caused by extended-spectrum-β-lactamase-producing Enterobacteriaceae: Importance of inadequate initial antimicrobial treatment. Antimicrob Ag Chemother 51:1987-1994, 2007

15. Schwaber MJ, Carmeli Y: Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in Enterobacteriaceae bacteraemia: A systematic review and meta-analysis. J Antimicrob Chemother 60:913-920, 2007

16. Zhanel GG, Karlowsky JA, Rubinstein E, et al: Tigecycline: A novel glycylcycline antibiotic. Expert Rev Anti Infect Ther 4:9-25, 2006

17. Babinchak T, Ellis-Grosse EJ, Dartois N, et al: The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections: Analysis of pooled clinical trial data. Clin Infect Dis 41:S354-S367, 2005 (suppl 5)

18. Ellis-Grosse EJ, Babinchak T, Dartois N, et al: The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: Results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. Clin Infect Dis 41:S341-S353, 2005 (suppl 5)

19. Gardiner D, Dukart G, Cooper A, et al: Safety and efficacy of intravenous tigecycline in subjects with secondary bacteremia: Pooled results from 8 phase III clinical trials. Clin Infect Dis 50:229-238, 2010

20. Curcio D, Vargas SW, Ugarte Ubiergo S, et al: Tigecycline treatment of critically ill patients: The Latin user experience. Curr Clin Pharmaco 6:18-25, 2011

21. Anthony KB, Fishman NO, Linkin DR, et al: Clinical and microbiological outcomes of serious infections with multidrug-resistant gram-negative organisms treated with tigecycline. Clin Infect Dis 46:567-570, 2008

22. Chemaly RF, Hanmod SS, Jiang Y, et al: Tigecycline use in cancer patients with serious infections: A report on 110 cases from a single institution. Medicine 88:211-220, 2009

23. Gaya H, Klastersky J, Schimpff SC, et al: Protocol for an international prospective trial of initial therapy regimens in neutropenic patients with malignant disease. Eur J Cancer 11:1-4, 1975 (suppl)

24. Clinical and Laboratory Standards Institute. 2007 Performance Standards for Antimicrobial Testing: Seventeenth Informational Supplement. CLSI document M100–S17. Wayne, PA, Clinical and Laboratory Standards Institute, 2007

25. European Committee on Antimicrobial Susceptibility Testing (EUCAST) Steering Committee. EUCAST technical note on tigecycline. Clin Microbiol Infect 12:1147-1149, 2006

26. Falagas ME, Karageorgopoulos DE, Dimopoulos G: Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of tigecycline. Curr Drug Metab 10:13-21, 2009

27. Reinert RR, Low DE, Rossi F, et al: Antimicrobial susceptibility among organisms from the Asia/Pacific Rim Europe and Latin and North America collected as part of TEST and the in vitro activity of tigecycline. J Antimicrob Chemother 60:1018-1029, 2007

28. Tasina E, Haidich AB, Kokkali S, et al: Efficacy and safety of tigecycline for the treatment of infectious diseases: A meta-analysis. Lancet Infect Dis 11:834-844, 2011

29. Yahav D, Lador A, Paul M, et al: Efficacy and safety of tigecycline: A systematic review and meta-analysis. J Antimicrob Chemother 66:1963-1971, 2011

30. Prasad P, Sun J, Danner RL, et al: Excess deaths associated with tigecycline after approval based on non-inferiority trials. Clin Infect Dis 54: 1699-1709, 2012

31. Gudiol C, Tubau F, Calatayud L, et al: Bacteraemia due to multidrug-resistant Gram-negative bacilli in cancer patients: Risk factors, antibiotic therapy and outcomes. J Antimicrob Chemother 66:657-663, 2011

32. Kang CI, Chung DR, Ko KS, et al: Risk factors for infection and treatment outcome of extended-spectrum beta-lactamase producing Escherichia coli and Klebsiella pneumoniae bacteremia in patients with hematologic malignancy. Ann Hematol 91:115-121, 2012

33. Carmeli Y, Akova M, Cornaglia G, et al: Controlling the spread of carbapenemase-producing Gram-negatives: Therapeutic approach and infection control. Clin Microbiol Infect 16:102-111, 2010

34. ECDC Antimicrobial Resistance and Healthcare-Associated Infections Programme. Antimicrobial resistance 2010: global attention on carbapenemase-producing bacteria. Euro Sourveil 15:46-49, 2010

35. European Conference on Infection in Leukaemia, Bacterial Resistance in Haematology–ECIL 4. Final version. February 14, 2012. ECIL Web Site: http://www.ebmt.org/Contents/Resources/Library/ECIL/Documents/ECIL4%202011%20Bacterial%20resistance%20in%20Haematology.pdf

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GLOSSARY TERMS

febrile neutropenia: symptoms include fever and a decrease in the number of neutrophils in the blood. A low neutrophil count increases the risk of infection.

Appendix

Inclusion and Exclusion Criteria

Consecutive adult patients with acute leukemia or lymphoma and other hematologic malignancies (undergoing conventional intensive chemotherapy or conditioning regimens for autologous hematopoietic stem-cell transplantation) were eligible to be randomly assigned if they had fever ($\geq$ 38.5°C on one occasion or $\geq$ 38°C on two or more occasions within 12 hours), chemotherapy-induced neutropenia (absolute neutrophils count $<$ 1,000 per cubic millimeter anticipated to decrease to fewer than 500 cells per cubic millimeter within 24 to 48 hours), and a presumed infection (ie, fever not likely to be due to a noninfectious cause such as drug or blood product administration). Patients were enrolled only once in the study and were hospitalized at the participating centers.

Patients were excluded from the trial if they had received any intravenous antibiotics during the preceding 96 hours, had a known allergy to any of the protocol antibiotics, had renal failure requiring hemo- or peritoneal dialysis or a serum creatinine level greater than 25 mL/min, were pregnant, or had known human immunodeficiency virus infection.

Randomization Procedure

Patients were centrally randomly assigned by using an automated computerized randomization procedure. The randomization list was created by using a computer random number generator program (Epistat, version 2) and was stratified by center and underlying disease with a 1:1 allocation by using a block size of eight. Participating centers were not aware of block size.

Treatment assignment was carried out directly by the Gruppo Italiano Malattie Ematologiche dell'Adulto centralized randomization system, using an Internet connection, a PC, and a modem. One set of envelopes was kept in each center to be used in case of computer failure or connection problems. After the investigator had obtained the patient's consent, he connected to the centralized randomization system for the allocation consignment.

Baseline and Follow-Up Assessments

After randomization, the empiric antibiotic treatment was started immediately at onset of fever. 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 and, in the presence of a central venous catheter, from catheter and peripheral vein) were performed before initiating the study antibiotics. Other cultures were performed as clinically indicated. After randomization, each patient was evaluated daily for adverse effects, and detailed clinical assessments were made at baseline and daily thereafter while the patient was being treated, as well as on the last day of treatment and 7 to 10 days after completion of therapy. Patients were evaluated for response as follows: at day 4 (between 72 and 96 hours) after empirical therapy initiation (early evaluation) when the results of baseline microbiologic cultures were available, and at the completion of the trial (overall evaluation). Antibiotic treatment was continued until success or failure was decided. The assigned therapy could only be modified before the 72 to 96 hours in the case of a worsening of the patient's clinical condition or in the case of an early documentation of an infection caused by a resistant pathogen otherwise the treatment modification earlier than 72 to 96 hours was considered a protocol violation.

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