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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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% of patients who had received combination therapy and monotherapy, respectively (127/187 vs. 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, 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. 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, a new emergence of gram negatives has occurred, and the diffusion of multidrug resistant (MDR) microorganisms has been observed. These new epidemiologic settings in neutropenic patients with cancer may be responsible for the inadequacy of the commonly used empiric monotherapy regimens, which has led to an increased mortality. 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 glycyclines, 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 Proteaceae.\(^{16-21}\) 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 (\(\geq 38.5^\circ C\) on one occasion or \(\geq 38^\circ C\) 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 antibiotic; 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 evaluable 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. 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-BioMerieux, Solna, Sweden), and the MIC breakpoints for susceptibility issued by the European Committee on Antimicrobial Susceptibility Testing (≤ 1 mg/L) were used.

**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, 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 performed on the 390 eligible patients revealed that a success rate of microbiologically documented infections was significantly higher in the combination group than in the monotherapy treated patients (61.4% vs 28.1%; \( P < .001 \)).

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% vs 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.

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**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% vs 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.
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...
carbapenem was significantly higher in the monotherapy than in the combination regimen (67 of 183, 36.6%; 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 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 ≥ 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 groups (12 of 187 in the monotherapy and 13 of 203 in the combination regimen). To estimate predictive factors at the univariable level, only the last two resulted independent risk factors at the multivariable level (Table 4).

### Table 2. Reasons for Failure

<table>
<thead>
<tr>
<th>Reasons for Failure</th>
<th>Pip/Tazo + Tigecycline (Assessable Patients Total Failures)</th>
<th>Pip/Tazo, Tigecycline (Assessable Patients Total Failures)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective</td>
<td>21 (43.8% of 48)</td>
<td>21 (41% of 52)</td>
</tr>
<tr>
<td>Persistent fever or relapsing fever</td>
<td>15 (31.3% of 48)</td>
<td>15 (29% of 52)</td>
</tr>
<tr>
<td>Progression of primary infection</td>
<td>6 (12.5% of 48)</td>
<td>6 (12% of 52)</td>
</tr>
<tr>
<td>Objective</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Persistent bacteremia</td>
<td>6 (12.5% of 48)</td>
<td>6 (12% of 52)</td>
</tr>
<tr>
<td>Resistant pathogen</td>
<td>5 (10.4% of 48)</td>
<td>5 (10% of 52)</td>
</tr>
<tr>
<td>Breakthrough bacteremia</td>
<td>3 (6.2% of 48)</td>
<td>3 (6% of 52)</td>
</tr>
<tr>
<td>Shock, ARDS, multiorgan failure</td>
<td>2 (4.3% of 48)</td>
<td>2 (4% of 52)</td>
</tr>
<tr>
<td>Withdrawal because of toxicity</td>
<td>5 (10.4% of 48)</td>
<td>5 (10% of 52)</td>
</tr>
<tr>
<td>Death as a result of the primary infection</td>
<td>3 (6.2% of 48)</td>
<td>3 (6% of 52)</td>
</tr>
<tr>
<td>Two or more reasons</td>
<td>5 (10.4% of 48)</td>
<td>5 (10% of 52)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Organism</th>
<th>Pip/Tazo Available for Analysis</th>
<th>Tigecycline Available for Analysis</th>
<th>Levofloxacin Available for Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organism</strong></td>
<td><strong>No. Resistant/Total No. %</strong></td>
<td><strong>No. Resistant/Total No. %</strong></td>
<td><strong>No. Resistant/Total No. %</strong></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>15/46 (33)</td>
<td>3/44 (7)</td>
<td>39/40 (97)</td>
</tr>
<tr>
<td>Pseudomonas spp</td>
<td>5/9 (55)</td>
<td>9/9 (100)</td>
<td>7/8 (87)</td>
</tr>
<tr>
<td>Klebsiella spp</td>
<td>4/11 (36)</td>
<td>1/10 (10)</td>
<td>10/10 (100)</td>
</tr>
<tr>
<td>Other Gram negative</td>
<td>2/6 (33)</td>
<td>0/3 (0)</td>
<td>2/4 (50)</td>
</tr>
<tr>
<td>Total gram-negativeorganisms</td>
<td>23/71 (32)</td>
<td>13/56 (23)</td>
<td>58/82 (94)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>3/7 (43)</td>
<td>1/7 (14)</td>
<td>2/6 (33)</td>
</tr>
<tr>
<td>MRSA</td>
<td>3/3 (100)</td>
<td>1/3 (33)</td>
<td>2/2 (100)</td>
</tr>
<tr>
<td>MSSA</td>
<td>0/4 (0)</td>
<td>0/4 (0)</td>
<td>0/4 (0)</td>
</tr>
<tr>
<td>Coagulase-negative Staphylococcus</td>
<td>58/82 (94)</td>
<td>4/58 (7)</td>
<td>51/61 (84)</td>
</tr>
<tr>
<td>MRCNS</td>
<td>53/53 (100)</td>
<td>3/43 (7)</td>
<td>37/45 (82)</td>
</tr>
<tr>
<td>MSCNS</td>
<td>5/9 (55)</td>
<td>1/15 (7)</td>
<td>14/16 (87)</td>
</tr>
<tr>
<td>Enterococcus spp</td>
<td>7/11 (64)</td>
<td>2/11 (18)</td>
<td>6/9 (67)</td>
</tr>
<tr>
<td>Streptococcus spp</td>
<td>1/10 (10)</td>
<td>0/8 (0)</td>
<td>10/12 (83)</td>
</tr>
<tr>
<td>Other Gram positive</td>
<td>2/4 (50)</td>
<td>2/5 (40)</td>
<td>3/3 (100)</td>
</tr>
<tr>
<td>Total gram-positive organisms</td>
<td>71/84 (75)</td>
<td>9/89 (10)</td>
<td>72/81 (79)</td>
</tr>
</tbody>
</table>

Abbreviations: ARDS, acute respiratory distress syndrome; Pip/Tazo, piperacillin/tazobactam.
The increase of relative proportion of bacteremias caused by gram negatives, and, at the same time the emergence of MDR microorganisms 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. 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, 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.

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

<table>
<thead>
<tr>
<th>Variables</th>
<th>Category</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic regimen</td>
<td>Monotherapy</td>
<td>2.86</td>
<td>1.59 to 4.12</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underlying disease</td>
<td>Acute leukemia</td>
<td>2.54</td>
<td>1.18 to 3.90</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td>Other hematologic</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

### Table 5. Mortality Rates in the Treated Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pip/Tazo + Tigecycline (N = 187)</th>
<th>Pip/Tazo (N = 203)</th>
<th>Absolute Difference in Risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>16/8.5</td>
<td>15/7.3</td>
<td>0.01 (0.04 to 0.06)</td>
<td>0.4</td>
</tr>
<tr>
<td>Death because of infection</td>
<td>11/5.8</td>
<td>11/5.4</td>
<td>0.004 (0.04 to 0.05)</td>
<td>0.5</td>
</tr>
<tr>
<td>Microbiologically documented infection with bacteremia</td>
<td>8/4.2</td>
<td>8/3.9</td>
<td>0.003 (0.03 to 0.04)</td>
<td>0.4</td>
</tr>
<tr>
<td>Single gram-negative isolate</td>
<td>5/2.7</td>
<td>3/1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klebsiella spp</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas spp</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single gram-positive isolate</td>
<td>2/1</td>
<td>2/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus spp</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus spp</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methicillin-resistant coagulase-negative Staphylococcus</td>
<td>—</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>1/0.5</td>
<td>3/1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E coli plus gram-positive organism</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-positive organisms only</td>
<td>—</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically documented infection</td>
<td>1/0.5</td>
<td>1/0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever of unexplained origin</td>
<td>—</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death because of fungal infection</td>
<td>2</td>
<td>1</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Death from noninfectious causes*</td>
<td>5/2.7</td>
<td>4/1.9</td>
<td>0.007 (0.02 to 0.03)</td>
<td>0.4</td>
</tr>
<tr>
<td>Bacteremia-related early death (death occurring within 72 hours from the start of empiric therapy)</td>
<td>1/0.5</td>
<td>4/2</td>
<td>−0.01 (0.03 to 0.007)</td>
<td>0.2</td>
</tr>
<tr>
<td>Single agent bacteremia*</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymicrobial bacteremia</td>
<td>0</td>
<td>1†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.
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 vs 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 \textit{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.\textsuperscript{26-30} However, no studies have been designed to evaluate the efficacy of tigecycline in bacteremias, although Chemaly\textsuperscript{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 \textit{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 \textit{E. coli} causing bacteremias account for up to 40%.\textsuperscript{14,15,31,32} At the same time, mortality and the delay of effective therapy have been associated with ESBL production in Enterobacteriaceae bacteremia.\textsuperscript{1,5,31,32} 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 carbapenem (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.\textsuperscript{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.\textsuperscript{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\textsuperscript{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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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 (≥ 38.5°C on one occasion or ≥ 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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