Lack of Ability of Ciprofloxacin-Rifampin Prophylaxis To Decrease Infection-Related Morbidity in Neutropenic Patients Given Cytotoxic Therapy and Peripheral Blood Stem Cell Transplants

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We compared ciprofloxacin alone with ciprofloxacin plus rifampin (C + R) as a prophylactic antibacterial regimen for 40 patients with solid tumors treated with high-dose chemotherapy and autologous stem cell transplantation support. No differences were found between groups in the time elapsed to the onset of fever, incidence of febrile episodes, amphotericin B use, and length of hospital stay. However, C + R combination prophylaxis significantly reduced the incidence of gram-positive bacteremia (five versus zero episodes) but was associated with a higher incidence of drug-related side effects.

Quinolone-based prophylaxis for patients treated with high-dose chemotherapy (HDC) and bone marrow transplantation has been associated with an important reduction in the incidence of gram-negative infection. Nevertheless, in most series 70 to 100% of patients developed fever during the neutropenic period despite the use of oral quinolones (10, 12, 16, 17). Furthermore, these studies did not demonstrate a reduction in gram-positive infection. In fact, there has been a shift in the relative distribution of the organisms that cause infection in neutropenic cancer patients, and gram-positive bacteria now account for 70% of all microbiologically documented infections (1–3, 5, 6, 13, 15, 19).

In recent years, several reports have addressed the question of improving prophylactic therapy by adding antibiotics with gram-positive coverage to a quinolone-based regimen (1, 4, 8, 9, 14). To explore the effectiveness of adding rifampin (R) to ciprofloxacin (C), we conducted a randomized prospective open-label clinical trial with adult patients with solid tumors treated with HDC and peripheral blood stem cell transplantation (PBSCT).

All patients scheduled to receive HDC with PBSCT rescue from July 1995 to August 1996 were eligible for the study. Patients were excluded if they had signs or symptoms of infection in the preceding 24 h, had received antibiotics within the previous 48 h, or had a history of allergy to quinolone derivatives or R. Patients were randomly assigned to receive a 500-mg tablet of C every 8 h or a 500-mg tablet of C every 8 h plus a 500-mg tablet of R every 12 h (C + R). Prophylaxis was begun 48 h before stem cell reinfusion and was continued until the development of the first episode of fever (defined as an axillary temperature of >38°C measured twice with a 4-h interval or a single temperature of >38.5°C), signs or symptoms of infection, serious adverse effects potentially attributable to the study drug, or recovery to an absolute neutrophil count of >500 × 10⁹ cells/liter. Once prophylaxis was stopped for any of these reasons, it was not resumed. Management of febrile episodes followed standard recommendations for this setting (11). Amphotericin B was started after 5 days of unexplained fever or for documented fungal infections. A second febrile episode was defined as a temperature rise after the patient was afebrile for 48 h or more after the first episode of fever.

Two blood specimen sets for culture were obtained from each patient with a new onset of fever and from patients who remained febrile 48 h after antibiotics had been started. Cultures were taken from the central line and from a peripheral vein and were inoculated in a BACTEC 6A.7A automated system (Becton Dickinson, Tow, N.Dak.). Other cultures were taken if clinically indicated. Bacteremia was defined as recovery of bacteria from one or more blood cultures. Identification of coagulase-negative staphylococcus bacteremia required the isolation of the bacteria in at least two or more separated blood cultures. Antibacterial susceptibility was tested by a microdilution assay (DIFCO FASCO; Difco Laboratories, Inc., Detroit, Mich.).

Adverse effects were attributed to the prophylactic regimen if they occurred during prophylaxis or within 48 h of the last dose without any other cause to account for them.

Forty-two patients were scheduled to receive HDC with PBSCT support consecutively during the study period. Two patients were excluded from the trial because they were treated with antibiotics before randomization. Forty patients were finally enrolled in the trial. Twenty patients were assigned to the C arm, and 20 were assigned to the C + R arm. The two groups were comparable in baseline characteristics (Table 1).

The time to onset of the first episode of fever (Fig. 1), incidence of febrile episodes, duration of fever, and length of hospital stay (Table 2) were similar for the two groups. The incidence of bacteremia as the initial infection event was not statistically different between the two groups: five episodes in the C group (four infections with coagulase-negative staphylococci and one with viridans streptococcus) and two in the C + R group (Enterobacter cloacae and Pseudomonas aeruginosa). However, there was a significant reduction in the incidence of gram-positive infection in the combination arm (five episodes with C and none with C + R; P < 0.05). All these strains were susceptible to R, and all but one were resistant to C. The two patients with gram-negative bacteremia in the C group were compliant with the prophylactic regimen, and the isolates were susceptible to C. No patient had a positive culture from the urine, stool, or any other body site.
No patient in this study had a severe infection or a serious systemic infectious complication (pneumonia, septic shock, or adult respiratory distress syndrome), and none died. Six patients had a second febrile episode (five in the C arm and one in the C + R arm; \( P = 0.18 \)). None of these episodes was microbiologically documented. These patients were still on antibiotics when they developed the second episode of fever. Two of these patients had signs of catheter insertion site infection, and both became afebrile with catheter removal. For the remaining three patients without apparent catheter infection, the catheter was removed because of persistence of fever after treatment with amphotericin B. In these three patients, fever subsided after catheter removal, although the blood counts of these patients were already recovering at that time. All catheter tip cultures were sterile. No patient had fever after antibiotic discontinuation. Four patients (two in each treatment arm) had catheter site clinical infection. In two patients this infection was complicated with fever. One patient had a catheter tip culture positive for *Escherichia coli*. All these infections were cured with catheter removal.

The proportions of patients requiring intravenous empirical antibiotic therapy (85% in each group) and the durations of antibiotic therapy for these patients (8.6 \( \pm \) 4.8 days in the C arm and 8.2 \( \pm \) 3.5 days in the C + R arm) were similar in the two groups. Six patients in the C arm and five in the C + R arm were treated with amphotericin B; none of these patients had documented fungal infection, and amphotericin B was used due to the persistence of fever (Table 2).

No patient in the C arm had adverse effects. C + R was considered the cause of adverse reaction in six patients (\( P < 0.05 \)). One patient had transient elevation in liver enzymes, and five patients had gastrointestinal complaints. These side effects were severe enough in three patients (15%) that medication was discontinued after 3 days for two of them and after 4 days for the third. None of these patients had a positive blood culture.

Over the last several years, gram-positive bacteria have be-

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**TABLE 1. Clinical characteristics of treatment groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value for group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>20</td>
</tr>
<tr>
<td>Mean age ± SD (yr)</td>
<td>40.2 ± 9.2</td>
</tr>
<tr>
<td>Male/female</td>
<td>2/18</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>17</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>0</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>1</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>2</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>0</td>
</tr>
<tr>
<td>Preparative regimen</td>
<td></td>
</tr>
<tr>
<td>STAMP Vơ</td>
<td>9</td>
</tr>
<tr>
<td>CbMTơ</td>
<td>9</td>
</tr>
<tr>
<td>Cb-VP16ơ</td>
<td>1</td>
</tr>
<tr>
<td>Cy-Cb-VP16ơd</td>
<td>0</td>
</tr>
<tr>
<td>BEACơ</td>
<td>1</td>
</tr>
<tr>
<td>TAX-Cb-VP16ơf</td>
<td>1</td>
</tr>
<tr>
<td>Hematopoietic growth factors</td>
<td>18</td>
</tr>
<tr>
<td>Mean duration of neutropenia ± SD (days)</td>
<td>8.7 ± 2.4 8.8 ± 1.7</td>
</tr>
<tr>
<td>Grade III–IV mucositis</td>
<td>6</td>
</tr>
<tr>
<td>Grade III–IV diarrhea</td>
<td>6</td>
</tr>
<tr>
<td>Days with central line</td>
<td>16.9 ± 2.2</td>
</tr>
</tbody>
</table>

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**TABLE 2. Fever and infection**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value for group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) of patients with fever</td>
<td>17 (85) 17 (85)</td>
</tr>
<tr>
<td>Days with fever (mean ± SD)</td>
<td>3 ± 1.8 3.8 ± 2.9</td>
</tr>
<tr>
<td>Days with antibiotics (mean ± SD)</td>
<td>8.6 ± 4.8 8.2 ± 3.5</td>
</tr>
<tr>
<td>No. (%) of patients requiring amphotericin B</td>
<td>6 (30) 5 (25)</td>
</tr>
<tr>
<td>Days with amphotericin B (mean ± SD)</td>
<td>6.8 ± 1.7 5 ± 2.8</td>
</tr>
<tr>
<td>No. (%) of patients requiring catheter removal</td>
<td>4 (20) 3 (15)</td>
</tr>
<tr>
<td>Days of hospital stay (mean ± SD)</td>
<td>18.3 ± 4.2 18.7 ± 2.5</td>
</tr>
</tbody>
</table>

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* There were no significant differences between the groups in any of the characteristics for which values are given in this table (\( P > 0.05 \)).

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**FIG. 1.** Kaplan-Meier plot showing the time between randomization and the onset of the first fever (\( P = 0.5 \) by the log rank test).
came the most common cause of infection in neutropenic patients. Coagulase-negative staphylococci are the cause of a high proportion of gram-positive infections, but viridans streptococci are now increasingly being reported as the cause of mild to severe bacteremic infections in these patients (2, 3, 5, 15, 19). Due to the increased incidence of gram-positive bacteremia and increasing concern about the course of these infections (6), some authors have postulated the inclusion of glycopenes in the initial empirical antibiotic regimen for fever and neutropenia (7, 18) and others have explored the inclusion of chemoprophylaxis against gram-positive infections.

Some investigators have reported a decrease in the frequency of gram-positive bacteremias when an antimicrobial agent with gram-positive coverage was added to a quinolone-based prophylactic regimen (4, 8, 9, 14). The combination of C + R compared with no prophylaxis decreased the occurrence of bacteremias (from 18 to 0%) and fever (from 98 to 57%) in a retrospective study of patients with breast cancer treated with HDC and bone marrow and PBSCSCT support (9). The addition of R to ofloxacin for bacterial prophylaxis in patients with hematological malignancies undergoing cytotoxic therapy for acute leukemia or bone marrow autografting has been shown in a recent randomized trial to reduce the incidence of gram-positive bacteremia without decreasing the number of febrile episodes (4).

The results of the current randomized study indicate that the addition of R to a quinolone regimen could reduce the incidence of documented gram-positive bacteremic infection without reducing the frequency of fever in neutropenic patients with solid tumors treated with HDC and PBSCSCT. Overall, five patients in this study had gram-positive blood cultures, and all of them had been allocated to the C arm. Unexpectedly, two patients in this study had gram-positive blood cultures, and all with solid tumors treated with HDC and PBSCT. Overall, five out of reducing the frequency of fever in neutropenic patients

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In contrast to previously published data, R was poorly tolerated in our study. Six patients (30%) had drug-related toxic reactions, including one patient with transient alteration in a liver function test and five patients with gastrointestinal symptoms. Side effects led to drug discontinuation for three patients. We did not observe resistance to R in gram-positive isolates, probably due to the short exposure to this agent. However, the emergence of gram-positive bacteria resistant to R could be of concern, especially for patients treated for longer periods, like those in multiple transplant programs, who have to receive prophylaxis more than once.

The results of this study imply that the reduction in the incidence of documented gram-positive infections with combined prophylactic regimens does not translate into a similar reduction in the incidence of other infection-related events. In our experience most gram-positive infections had a mild course. In fact, most authors have reported that coagulase-negative staphylococcal infections are rarely as acutely devastating as gram-negative infections (2, 3, 5).

Reduction of the incidence of fever during neutropenia, which can facilitate outpatient care and reduce morbidity and costs, must be the goal of future studies in this setting.