Randomized Trial of Oral Versus Intravenous Antibiotics in Low-risk Febrile Neutropenic Patients with Lung Cancer

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Background: Neutropenic fever is one of the most serious adverse effects of cancer chemotherapy. Neutropenia may cause a life-threatening bacterial infection. Therefore, febrile neutropenic inpatients are empirically treated with intravenous broad-spectrum antibiotics. Recently, several studies have suggested the presence of low-risk groups among febrile neutropenic patients.

Methods: A prospective randomized trial was conducted to compare treatment with oral ciprofloxacin (200 mg) and amoxicillin-clavulanate (375 mg) administered every 8 h against that with intravenous ceftazidime (1 g) administered every 12 h in low-risk febrile neutropenic patients with lung cancer. All patients received chemotherapy and antibiotic therapy while being hospitalized.

Results: A total of 177 patients with lung cancer agreed to participate in this study prior to undergoing chemotherapy. Among them, a total of 36 neutropenic patients with 42 febrile episodes were enrolled in the study. Treatment was successful without the need for modification in 91% of the episodes in patients receiving the oral regimen and 79% of the episodes in patients receiving the intravenous regimen. No treatment-related deaths occurred. One patient developed nausea while receiving the oral regimen, so the oral regimen was changed to the intravenous regimen in this patient.

Conclusions: This prospective study suggested that treatment with oral antibiotics ciprofloxacin plus amoxicillin-clavulanate was effective for low-risk febrile neutropenic patients after chemotherapy.

Key words: oral antibiotics – low-risk – febrile neutropenia

INTRODUCTION

Neutropenic fever is one of the most serious adverse effects in cancer chemotherapy. Neutropenia may cause a life-threatening bacterial infection. The risk of infection increases in patients with a neutrophil count of <1000/mm³ (1). As a result, most cancer patients remain in hospital after undergoing chemotherapy in Japan, and empirical broad-spectrum intravenous antibiotics are administered to febrile neutropenic patients. This approach is effective in reducing morbidity and mortality but is associated with toxicity related to intravenous antibiotics, as well as physical and psychological discomfort for the patient. In addition, parenteral antibiotic administration requires insertion of an intravenous catheter, which carries a risk of infection. Prolonged hospitalization may cause infection to drug-resistant organisms, is expensive, and has a detrimental effect on quality of life.

Recently, several studies have suggested the presence of low-risk groups among febrile neutropenic patients (2–4). Medical complications were less frequent overall for patients whose neutropenia (<500/mm³) resolved in 7 days or less, compared to other patients (4). A study demonstrated that neutropenia lasted for 1 week or less in 85% of the patients selected using the following exclusion criteria: hepatic insufficiency (alanine aminotransferase activity > four times normal), a history of recurrent pyrexia of undetermined origin (PUO), shock (systolic blood pressure <80 mmHg or peripheral circulatory failure), any other comorbid conditions requiring hospitalization (except for anemia or thrombocytopenia) and the expectation of prolonged neutropenia (>7 days) based on the presence of aplastic anemia, myelodysplasia, leukemia or other causes (5). Patients who did not meet any of these exclusion criteria were considered to belong to a low-risk group. A randomized trial comparing oral ciprofloxacin and amoxicillin-clavulanate with...
Oral antibiotics in low-risk patients

intravenous aztreonam and clindamycin was conducted in these low-risk febrile neutropenic patients (6). This trial demonstrated that oral antibiotics were as effective as intravenous ones.

We conducted a randomized trial to compare oral ciprofloxacin and amoxicillin-clavulanate with intravenous ceftazidime, which was empirically used, in low-risk febrile neutropenic patients with lung cancer. The combination of ciprofloxacin and amoxicillin-clavulanate provides sufficient coverage against gram-negative enteric bacilli and gram-positive cocci. The aim of our trial was to determine whether an oral regimen was an acceptable alternative to an intravenous regimen in low-risk patients.

PATIENTS AND METHODS

CRITERIA FOR ELIGIBILITY

Eligible patients included those with lung cancer and neutropenia after having undergone platinum-based chemotherapy. Patients were required to have a single axillary temperature of 37.5°C or higher after platinum-based chemotherapy, an absolute leukocyte count ≤1000/mm³ or a neutrophil count ≤500/mm³. Other criteria included an age of 20 years or more and an ECOG performance status (PS) of between 0 and 2 (inclusive). The exclusion criteria included the following conditions: previous anaphylactic reactions or hypersensitivity to any of the antibiotics used or related products; antibiotic treatment within the preceding 96 h; prior administration of nonsteroidal anti-inflammatory drugs (NSAIDs); recurrent PUO; renal insufficiency (serum creatinine ≥2.5 mg/dl or need for dialysis); hepatic insufficiency (aspartate aminotransferase/alanine aminotransferase levels > four times the normal value); systolic blood pressure ≤90 mmHg or peripheral circulatory failure; uncontrolled hypercalcemia; altered sensorium; respiratory rate ≥30 breaths/min; serum sodium ≤128 mg/dl; and the inability to take oral medications because of painful mouth ulcers, intestinal malabsorption or severe nausea and vomiting. All patients were required to provide their written informed consent prior to undergoing chemotherapy, and the institutional review board at the National Cancer Center approved the study’s protocol.

TREATMENT PLAN

All patients received chemotherapy and antibiotic therapy on an inpatient basis. The baseline evaluation included a physical examination (blood pressure, pulse and respiratory rate, temperature). Cultures were obtained of blood, sputum, throat, urine and feces (anal swabs). Patients were randomly assigned to one of two regimens using consecutive sealed envelopes. The oral regimen consisted of ciprofloxacin (200 mg) plus amoxicillin-clavulanate (375 mg) administered every 8 h, while the intravenous regimen consisted of ceftazidime (1 g) administered every 12 h. Granulocyte colony-stimulating...
factor (G-CSF) support was allowed. The administration of NSAIDs was not allowed. The administration of aluminum- and magnesium-containing antacids and oral iron preparations was allowed if they were administered more than 3 h after the administration of ciprofloxacin. The use of other antibiotics was prohibited during the trial.

**DIAGNOSTIC CRITERIA AND EVALUATION**

Each febrile episode was classified as either a clinically or microbiologically documented infection or PUO. Microbiologically documented infection necessitated the isolation of a bacterial pathogen from blood, urine, pus or exudates, along with clinical, laboratory or radiographic evidence of infection at the same site. Clinical infection was diagnosed when clear evidence of an infection was present but an organism could not be isolated. PUO was defined as the requisite temperature elevation with no clinical or microbiologic evidence of infection within 72 h of enrolment in the study.

Clinical outcomes were evaluated at 48 h and 7 days after the start of antibiotic treatment. Each patient was physically examined every day. Patients who remained febrile (without a downward trend) after 48 h or who had a body temperature ≥37°C on day 7 were removed from the study and treated with appropriate therapy; antibiotic treatment in these patients was considered to have failed. Treatment outcome was classified into three categories (7). ‘Success without modification’ referred to episodes in which the patient successfully recovered from fever and neutropenia without the need of additional antimicrobial agents or the modification of the initially assigned regimen. ‘Success with modification’ referred to episodes in which the patient successfully recovered from the fever and neutropenia but required a modification of the initially assigned regimen. ‘Failure’ referred to all other cases. The response rate was defined as the percentage of ‘success without modification’ cases among all eligible patients.

**STATISTICAL ANALYSIS**

Assuming a response rate to the intravenous regimen of 80%, the study was designed to enroll 63 patients per treatment arm to ensure that the oral regimen would not be 20% worse (i.e. 60%) at a level of significance alpha = 0.05 and 80% power using a two-sided chi-square test. An interim analysis was

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Oral ciprofloxacin and amoxicillin-clavulanate</th>
<th>Intravenous ceftazidime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible episodes</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Age (year)</td>
<td>68 (54–76)</td>
<td>67 (51–75)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male/female 15/7</td>
<td>15/4</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>6/16</td>
<td>2/17</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Past</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Current</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Smoking index</td>
<td>Median (range) 910 (0–3480)</td>
<td>880 (0–2400)</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
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<tr>
<td>Adenocarcinoma</td>
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<td>7</td>
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<tr>
<td>Squamous cell carcinoma</td>
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<td>4</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
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<td>2</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Absolute neutrophil count (at randomization)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤100/μm³</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>101–500/μm³</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>501–1000/μm³</td>
<td>5</td>
<td>7</td>
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<tr>
<td>Duration of neutropenia after randomization (days)</td>
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<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>4 (2–7)</td>
<td>4 (2–12)</td>
</tr>
<tr>
<td>Treatment with G-CSF [no. (%)]</td>
<td>19 (86)</td>
<td>14 (74)</td>
</tr>
</tbody>
</table>
planned at an accrual level of 40 patients. If a significant difference in response rates \( (P < 0.01) \) was observed, or if septic shock appeared in more than 10% of the patients undergoing the oral regimen, the study was to be terminated. Comparisons between proportions were done using a Pearson chi-square test or a Fisher exact test, when appropriate.

**RESULTS**

**PATIENT POPULATION AND TREATMENT**

A total of 177 patients with lung cancer agreed to participate in this study prior to undergoing chemotherapy between May 1995 and February 2001. Among them, a total of 36 neutropenic patients with 42 febrile episodes were enrolled in the study. One episode was ineligible because of hyponatremia. Of the 41 episodes (in 35 patients) included in the analysis, four patients were enrolled more than once: three patients had two episodes each, and one patient had four episodes. The patient characteristics are listed in Table 1. Twenty-two episodes were assigned to the oral regimen and 19 episodes were assigned to the intravenous regimen (Fig. 1). No statistically significant difference was seen between the two groups with regard to age, gender, PS, smoking status, histologic subtype and absolute neutrophil count. During 33 episodes, G-CSF was administered in addition to the assigned treatment. The median duration of neutropenia was 4 days in both groups.

**EVALUATION BEFORE ANTIBIOTIC THERAPY**

PUO was observed in approximately two-thirds of all febrile episodes. Infection was documented in 15 episodes. Most documented infections consisted of bronchus or lung infections (10 episodes) or urinary tract infections (three episodes). Other infections included colitis and alveolar pyorrhea. Microbiological pathogens were detected in five episodes. *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae* were isolated from sputum and *Pseudomonas aeruginosa* and *Enterococcus faecalis* were isolated from urine.

**EFFICACY**

The response rates were similar in the two groups (91% versus 79%, \( P = 0.39 \)) (Table 2). PUO was successfully treated in all 26 episodes. On the other hand, documented infection was successfully treated in 60% of the patients (four out of six episodes in patients receiving the oral regimen and five out of nine episodes in patients receiving the intravenous regimen). A total of six patients received changes to their treatment regimen. Two patients in the oral regimen group were switched to piperacillin sodium or ceftazidime. Four patients in the intravenous regimen group were switched to carbapenem with or without the addition of clindamycin or amikacin.

In approximately half of the episodes in both groups, the fever disappeared by day 4 of the treatment. By day 8, the fever had resolved in 90% of all episodes.

**ADVERSE EFFECTS**

Few adverse effects were encountered. One patient developed nausea while receiving the oral regimen. The oral regimen was therefore changed to an intravenous regimen (piperacillin sodium) in this patient.

**DISCUSSION**

Febrile neutropenia can be a life-threatening complication of cancer chemotherapy. Therefore, febrile neutropenic patients are usually hospitalized for the administration of empiric, broad-spectrum, intravenous antibiotic therapy. Several analyses have demonstrated that febrile neutropenic patients comprise heterogeneous subgroups among which are low-risk patients with a high response rate to antibiotic therapy and a low risk of serious complications (2–4). We conducted a randomized trial to compare the oral administration of ciprofloxacin and amoxicillin-clavulanate with the intravenous administration of ceftazidime in low-risk febrile neutropenic patients with lung cancer. However, this study was terminated in February 2001 because of slow enrolment and the publication of two large randomized trials comparing oral with intravenous antibiotic therapy for low-risk febrile patients who developed neutropenia during cancer chemotherapy (8,9). In one trial, oral ciprofloxacin plus amoxicillin-clavulanate was compared with intravenous ceftazidime (8). These regimens were almost identical to those in our trial. In the other trial, oral ciprofloxacin plus amoxicillin-clavulanate was compared with intravenous ceftriaxone plus amikacin (9). Both trials demonstrated that oral therapy with ciprofloxacin plus amoxicillin-clavulanate was as safe and effective as intravenous therapy. Our trial confirmed these results, in spite of the smaller sample size.
The selection of low-risk patients with febrile neutropenia is very important. A multinational trial demonstrated that predictive factors for low risk complications included a burden of illness indicating the absence of symptoms or the presence of mild symptoms [weight, 5; odds ratio (OR), 8.21] or moderate symptoms (weight 3; OR, 3.70); the absence of hypotension (weight, 5; OR, 7.62); the absence of chromic obstructive pulmonary disease (COPD) (weight, 4; OR, 5.35); the presence of a solid tumor or the absence of previous fungal infection in patients with hematologic malignancies (weight, 4; OR, 5.07); an outpatient status (weight, 3; OR, 3.51); the absence of dehydration (weight, 3; OR, 3.81); and an age <60 years (weight, 2; OR, 2.45). A risk-index score ≥21 was considered to indicate a low-risk (10). In our trial, all of the enrolled patients had solid tumors (lung cancer) without hypotension or dehydration and no or mild symptoms. All but one patient had no COPD, producing a risk score of 21 or greater.

PUO was observed in 63% of the low-risk febrile neutropenic patients. The PUO percentage was identical to that reported in previous trials. All patients with PUO were successfully treated with oral or intravenous antibiotic therapy in our trial. Oral ciprofloxacin plus amoxicillin-clavulanate was effective for the treatment of PUO. Documented infections were successfully treated with an oral regimen in four out of six episodes and with an intravenous regimen in five out of nine episodes. Six patients needed to modify their regimen to an intravenous regimen containing cephalosporin or carbapenem. Oral ciprofloxacin plus amoxicillin-clavulanate was also effective in selected low-risk patients with documented infections.

Oral antibiotics produced a successful outcome in 91% of the patients, although 86% of the patients also received G-CSF support. Whether G-CSF support is needed in low-risk patients remains uncertain. The clinical practice guidelines of the American Society of Clinical Oncology recommend that G-CSF should not be routinely used as adjunct therapy for the treatment of uncomplicated fever and neutropenia (11). Uncomplicated fever and neutropenia are defined as follows: fever of ≤10 days in duration; no evidence of pneumonia, cellulitis, abscess, sinusitis or hypotension; and no uncontrolled malignancies. Oral antibiotics with ciprofloxacin plus amoxicillin-clavulanate are probably effective even if G-CSF support is not performed and can be easily administered to febrile neutropenic outpatients. In a randomized trial, oral antibiotics (ciprofloxacin plus amoxicillin-clavulanate) with early hospital discharge was compared with inpatient intravenous antibiotics (gentamicin plus tazocin) for the treatment of low-risk febrile neutropenic patients with cancer (12). This study suggested that oral antibiotics with early discharge was feasible and an alternative to conventional intravenous antibiotic regimens.

In conclusion, our trial suggested that oral antibiotic therapy with ciprofloxacin plus amoxicillin-clavulanate is effective for the treatment of low-risk febrile neutropenic patients, although the trial was prematurely terminated because of slow enrollment.

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References