Clinical Research Paper

Correlation of fever to infection in patients with chemotherapy-induced neutropenia

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Key words: neoplasm, chemotherapy, neutropenia, fever, infection

Background and Objective: The cancer patients with chemotherapy-induced neutropenia often suffer from fever and infection, but current opinions on the correlation of the fever to infection are controversial. This study aimed to investigate the incidence and correlation of fever and infection in cancer patients with chemotherapy-induced neutropenia. Methods: Clinical data of 256 in-patients with chemotherapy-induced neutropenia from January to July 2007 were analyzed. The occurrence of fever and infection in these patients were analyzed by using descriptive analysis and agreement test. Results: Of the 256 patients, 100 (39.1%) suffered from fever, and 42 (16.4%) experienced infection. The temperature of febrile patients was (39.0 ± 0.64)°C. The main sites of infection were the pharynx (42.9%), oral cavity (21.4%) and low respiratory tract (14.3%). The consistency rate was 0.75 between fever and infection (Kappa = 0.414, p < 0.001). Conclusion: The incidence of fever and infection in cancer patients with chemotherapy-induced neutropenia are high with a moderate agreement between fever and infection.

The cancer patients with chemotherapy-induced neutropenia often suffer from fever and infection. However, current opinions on the correlation of the fever to infection in cancer patients are controversial, which would directly influence the medication choice. Therefore, we followed up 256 cancer patients who suffered from chemotherapy-induced neutropenia, aimed to explore the incidence and correlation of fever and infection.

Materials and Methods

Subjects. A total of 256 cancer patients who suffered from chemotherapy-induced neutropenia were treated Zhejiang Provincial Cancer Hospital from January to July in 2007, including 76 men (29.7%) and 180 women (70.3%). The median age was 51 years (range, 16–81 years); 57 (22.3%) patients were aged of ≥60 years. The main types of cancers were breast cancer and lung cancer, accounting for 48.0% (123 cases) and 24.2% (62 cases); the rest cancers included 14 cases (5.5%) of ovarian cancer, 13 cases (5.1%) of malignant lymphoma, 11 cases (4.3%) of gastric cancer, 10 cases (3.9%) of nasopharyngeal carcinoma, eight cases (3.1%) of cervical cancer, five cases (2.0%) of esophageal carcinoma and ten cases (3.9%) of other cancers. The chemotherapeutic drugs included taxol, docetaxel, vinorelbine, vincristine, doxorubicin, pharorubicin, pirarubicin, gemcitabine, cyclophosphamide, ifosphamide, nedaplatin, oxaliplatin, cisplatin, carboplatin, 5-fluorouracil and etoposide. Of the 256 patients, 232 (90.6%) were treated with combined chemotherapy, 24 (9.4%) were treated with a single medication.

Detection criteria. Neutropenia refers to a condition in which the absolute value of neutrophils is below 0.5 x 10^9/L.1 According to the National Comprehensive Cancer Network (NCCN) detection criteria, fever refers to the condition in which a single measurement of oral temperature ≥38.3°C or the condition of oral temperature ≥38.0°C lasts for 1 h.2 In this study, the cases of fever caused by non-infective factors, such as tumor itself, drug, blood product infusion or graft-versus-host disease, were excluded. Infection was diagnosed in accordance with “Hospital infection diagnostic criteria”35 issued by Ministry of Public Health in 2001, including clinical diagnosis and the cases with positive experimental diagnosis, while excluding the infection, which had already existed before the occurrence of neutropenia.

Statistical analysis. All data were analyzed using SPSS 13.0 software. The occurrence condition was presented as rate, and the composition was shown by proportion. The correlation of fever to infection was analyzed by Kappa consistency test.

Results

The clinical characteristics of the patients with fever. Among the 256 patients with chemotherapy-induced neutropenia, 100 (39.1%) suffered from fever, including 28 (28.0%) men and 72 (72.0%) women with a median age of 51 years (range, 25–72 years). Of the 100 fever patients, 52 (52.0%) had breast cancer and 22 (22.0%) had lung cancer; 92 (92.0%) received combined chemotherapy and eight (8.0%) received docetaxel single medication. The chemotherapeutic drugs were mainly docetaxel, taxol and pharorubicin. The
occurrence of fever was detected at 2–21 days after chemotherapy, averaging at day 7. The mean body temperature for the patients with fever was $(39.0 \pm 0.6) ^\circ C$, with a maximum of $41.5 ^\circ C$, including 52 cases (52.0%) of hyperpyrexia and one case (1.0%) of ultrahyperpyrexia. The fever pattern was irregular fever. The mean duration of fever was three days and 53 (53.0%) patients experienced over two days of fever. Fourteen patients had received no antibiotic treatment; the antibiotics taken by the other 86 patients were mainly fluorine quinolones (levofloxacin), beta-lactam (penicillin and the second, third and fourth generations of cephalosporins) and antifungal drugs (fluconazol). Among the 100 patients with fever, 30 experienced no other symptoms except fever. Thirty-five samples collected from fever patients were cultured, and 13 (37.1%) of them were positive.

The clinical characteristics of the patients with infection. Among the 256 patients, 42 (16.4%) suffered from infection, including 14 (33.3%) men and 28 (66.7%) women, with a median age of 51 years. On average, infection was detected at day 7. The main sites of infection included the pharynx, oral cavity and lower respiratory tract (Table 1). For the two cases of combined infection, the lower respiratory tract and oral cavity were involved in one case, the respiratory tract and blood were involved in the other case. Both patients were died. Samples from 26 infection patients were cultured, and 17 (65.4%) of them were positive. Nineteen pathogen strains were detected, including ten strains (52.6%) of Monilia albicans three strains (15.8%) of Pseudomonas aeruginosa, two strains (10.5%) of Escherichia coli, one strain (5.3%) of Staphylococcus aureus, one strain (5.3%) of meticillin sodium-resistant Staphylococcus haemolyticus, one strain (5.3%) of baumannii and one strain (5.3%) of Klebsiella pneumoniae.

The consistency between fever and infection cases. Among the 42 patients with infection, except for one patient with oral infection, the other patients all experienced fever to different degrees (the body temperature of two patients did not reach NCCN criteria for the diagnosis of fever). Among the 100 patients with fever, 39 also had infection. The consistency between fever and infection was moderate, with a consistency rate of 0.75 (Kappa = 0.414, p < 0.001) (Table 2).

### Discussion

In our study, the occurrence rate of fever in the patients with chemotherapy-induced neutropenia was 39.1%; while Dale reported that the occurrence rate of febrile neutropenia was 25–40% in the patients who had received chemotherapy. Among the 256 patients in this study, most breast cancer patients were treated with regimens containing taxol or docetaxel, a kind of cytotoxic antitumor drug. As a new type of anti-microtubule drug, it could promote polymerization and inhibit depolymerization of microtubule proteins to maintain the stability of microtubule proteins and inhibit cell mitosis. Neutropenia is the most common adverse event, and is usually serious.

The occurrence rate of infection in this study was 16.4%. This rate is much higher than the average value (3.4%) for the hospitalization patients in Zhejiang Provincial Cancer Hospital during the same period, indicating that cancer patients with neutropenia are a high-risk group for hospital-acquired infection. However, this rate is lower than the reported infection rate (40–60%) in domestic neutropenia patients. The infection mainly involved the respiratory tract and oral cavity, which are consistent with previous reports. In our study, infection occurred at seven days, on average, after chemotherapy, which was basically in line with the occurrence of fever; the positive rate of pathogens in samples from 26 infection patients was 65.4%, much lower than that in samples from the patients with hospital-acquired infection during the same period (84.1%). The pathogens mainly included fungus (52.6%), followed by Gram-negative bacillus (36.8%) and Gram-positive coccus (10.5%). While Liu et al. reported that the pathogens of bacterial infection mainly were Gram-negative bacillus, followed by Gram-positive coccus and fungus. An increase of Gram-positive coccus infection, even higher than Gram-negative bacillus infection, had also been reported. According to our results, the infection in neutropenia patients was mainly composed of endogenous infection caused by conditioned pathogen; the fungus contribution much higher than bacterial contribution might caused by the wide application of broad-spectrum antibiotics, routine use of corticosteroid hormone such as dexamethasone during chemotherapy, and increased occurrence of deep fungal infection as a result of mucosal barrier destruction by chemotherapy. Therefore, we recommend to adopt experience-based antibiotic therapy for the patients with potential infection according to the common microbial population in the hospital and related efficient drugs; the therapeutic regimen should be adjusted when the pathogen and the results of drug-sensitivity test are confirmed.

### Table 1  Infection sites in cancer patients with chemotherapy-induced neutropenia

<table>
<thead>
<tr>
<th>Site</th>
<th>Cases</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharynx</td>
<td>18</td>
<td>42.9</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>9</td>
<td>21.4</td>
</tr>
<tr>
<td>Low respiratory tract</td>
<td>6</td>
<td>14.3</td>
</tr>
<tr>
<td>Skin</td>
<td>3</td>
<td>7.1</td>
</tr>
<tr>
<td>Compound</td>
<td>2</td>
<td>4.8</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
<td>9.5</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>100.0</td>
</tr>
</tbody>
</table>

### Table 2  The agreement test of fever and infection cases

<table>
<thead>
<tr>
<th>Infecction</th>
<th>Yes</th>
<th>Fever</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>39</td>
<td>3</td>
<td>153</td>
<td>214</td>
</tr>
<tr>
<td>No</td>
<td>61</td>
<td>156</td>
<td>153</td>
<td>214</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>156</td>
<td>153</td>
<td>256</td>
</tr>
</tbody>
</table>

Kappa = 0.414, p = 0.001.
sample collection rate in fever patients was rather low in this study (this needs further investigation), therefore, infection might exist in those with fever of unknown etiology. However, 14.0% of the fever patients in this study received no antibiotic treatment, while their body temperature returned to normal when the neutrophil levels recovered after the administration of granulocyte colony-stimulating factor; fever lasted for less than two days in 47.0% of the fever patients, indicating the possibility of non-infection fever in some patients with fever of unknown etiology. Currently, the mechanism of non-infection fever in neutropenia patients is unclear, however, the term granulocytopenia fever is used in Chinese clinical practice, which might be based on the decrease of lymphocytes in granulocytopenia patients. This phenomenon and fever mechanism needs to be further investigated. Among the 42 patients with infection in this study, except for one patient with oral infection, the others suffered from fever to different degrees; the consistency between fever and infection was moderate. Therefore, we recommend to adopt overall infection-related inspection for fever patients, including symptoms, syndromes, imaging examination, and microbiological test, followed by corresponding therapy and nursing care.

References