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ORIGINAL ARTICLE

Drug fever after cancer chemotherapy is most commonly observed on posttreatment days 3 and 4

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Abstract
Background This study was undertaken to analyze the characteristics of fever after cancer chemotherapy in order to reduce unnecessary medical care.
Methods Retrospectively, 1016 consecutive cycles of cancer chemotherapy were analyzed. Fever was defined as a temperature of ≥37.5 °C lasting for 1 h. Age, sex, tumor histology, the treatment regimen, the timing of fever onset, the number of days for which the fever persisted, the cause of the fever, the presence or absence of radiotherapy, and the use of granulocyte colony-stimulating factor (G-CSF) were examined.
Results The patients included 748 males and 268 females (median age = 68, range = 29–88), of whom 949, 52, and 15 were suffering from lung cancer, malignant pleural mesothelioma, and other diseases, respectively. Fever was observed in 367 cycles (36 %), including 280 cycles (37 %) involving males and 87 cycles (32 %) involving females. Fever occurred most commonly in the first cycles and was higher than later cycles (41 vs. 30 %, $p < 0.001$). Fever occurred most frequently on posttreatment days 4 (8 %), 3 (7 %), and 12 (7 %), and the distribution of fever episodes exhibited two peaks on posttreatment days 3 and 4 and 10–14. Fever on posttreatment days 3 and 4 was most commonly observed in patients treated with gemcitabine (20 %) or docetaxel (18 %). The causes of fever included infection (47 %; including febrile neutropenia [24 %]), adverse drug effects (24 %), unknown causes (19 %), and tumors (7 %). Radiotherapy led to a significant increase in the frequency of fever (46 vs. 34 %, $p < 0.001$). Thirty-three percent of patients received G-CSF, and the incidence ratios of fever in patients who received G-CSF were higher than those who did not receive G-CSF (44 vs. 31 %, $p < 0.001$).
Conclusion The febrile episodes that occurred on posttreatment days 3 and 4 were considered to represent adverse drug reactions after cancer chemotherapy. Physicians should be aware of this feature of chemotherapy-associated fever and avoid unnecessary examination and treatments including prescribing antibiotics.

Keywords Cancer chemotherapy · Drug fever · Radiotherapy

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Introduction

Research on fever after cancer chemotherapy has mainly focused on the management of infections because serious infections that develop in neutropenic cancer patients who are receiving cytotoxic chemotherapy [1–3] and with angiogenesis inhibitors like bevacizumab [4] can have significant consequences. However, fever is the sole symptom in 3 to 6 % of cases of adverse drug reactions [5–8], and the risk of developing drug fever increases with the number of drugs prescribed. In cases of drug fever after cancer chemotherapy, if antibiotics are prescribed due to a fear of infection, the patient's fever will not improve and could become worse, which could result in undesirable consequences including extra

testing, unnecessary therapy, a longer hospital stay, and the development of drug-resistant bacteria. Despite the importance of drug fever after cancer chemotherapy, there has been little research about it, and there are no reliable data about its incidence.

Thus, we conducted a retrospective analysis of episodes of fever that occurred after cancer chemotherapy. The main objectives of this study were to determine the characteristics of such fever episodes and to find a way of discriminating between drug and neutropenic fever after cancer chemotherapy.

Patients and methods

The subjects selected for this study were consecutive admitted patients treated at the Department of Respiratory Medicine, Kawasaki Medical School Hospital, between April 2004 and March 2007, or at the Division of Respiratory Disease, Department of Internal Medicine, Nagasaki Municipal Hospital, between April 2007 and December 2008. The inclusion criteria were patients who were diagnosed with thoracic malignancies including lung cancer, malignant thoracic mesothelioma, thymic cancer, primary unknown cancer, and hemangiosarcoma and received chemotherapy. Fever was defined as a temperature of ≥37.5 °C lasting for 1 h. The patients' age and sex, the histology of the tumor, the treatment regimens employed, the timing of fever onset, the number of days for which the fever persisted, the cause of the fever, the use of granulocyte colony-stimulating factor (G-CSF), and the presence or absence of radiotherapy for primary or metastatic lesions were recorded. The incidence of fever on posttreatment days 3 and 4 was defined as the percentage of cycles in which fever developed on posttreatment day 3 or 4. We then retrospectively analyzed the characteristics of the fevers experienced by patients with thoracic malignancies after chemotherapy. The diagnosis of infection was fundamentally based on culture; however, principal physicians including supervisors eventually decided under whole clinical stage. The chi-square test and Fisher's exact test were used to evaluate the differences between groups.

Results

One thousand and sixteen chemotherapy cycles were analyzed. The patients' characteristics are shown in Table 1. Seventy-four percent of the patients (748 of 1016) were males, the patients' median age was 68 years (range from 29 to 88 years), and lung cancer was the most common disease (93 %).

Fevers occurred in 36 % of cycles (367 of 1016) including 37 % of those involving males and 32 % of those involving females. There was no difference in the frequency of fever among the sexes ($p = 0.146$). The incidence of fever according to age was 33 % (≤60), 41 % (61–65), 36 % (66–70), 33 % (71–75), 41 % (76–80), and 33 % (≥81); it did not differ significantly with age ($p = 0.424$). The incidence of fever according to chemotherapy cycle was 41 % in the first (236/576), 31 % in the second (74/236), 30 % in the third (35/116), 28 % in the fourth (16/57), 22 % in the fifth (4/18), 13 % in the sixth (1/8), 25 % in the seventh (1/4), and 0 % in the eighth (0/1); it differed significantly between the first and subsequent cycles ($p < 0.001$).

Table 1 Patient characteristics

Characteristics	Number of cycles
Total	1016
Gender	
Male	748
Female	268
Age (years)	
Median	68
Range	29–88
Disease	
Lung cancer	949
Malignant pleural mesothelioma	52
Others	15
Radiotherapy	
Yes	194
No	822

Antitumor agents

In incidence of fever according to the drugs administered, gemcitabine was the drug that was most frequently associated with fever (41 %; 43/106), followed by irinotecan (40 %; 108/272), amrubicin (39 %; 29/75), docetaxel (36 %; 47/131), vinorelbine (34 %; 14/41), paclitaxel (34 %; 50/149), carboplatin (33 %; 113/339), gefitinib (33 %; 21/63), etoposide (30 %; 9/30), cisplatin (29 %; 82/284), pemetrexed (28 %; 22/78), nedaplatin (27 %; 9/34), and S-1 (23 %; 11/47). There were no patients who received monoclonal antibodies.

Posttreatment days

Figure 1 shows the incidence of fever on each posttreatment day. Posttreatment days 4 (8.3 %), 3 (6.8 %), and 12 (6.7 %) were the days on which fever was most common. The distribution of fever exhibited a bimodal distribution, i.e., while it peaked on posttreatment days 3 and 4; otherwise, it generally gradually increased until day 12 and then gradually decreased. The peak on posttreatment days 3 and 4 was considered to be due to adverse drug reactions, and the latter peak was

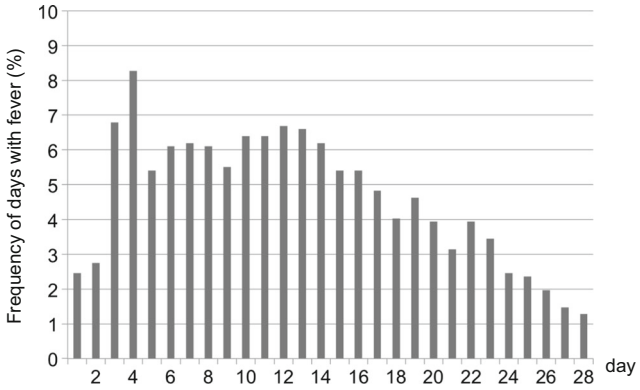

Fig. 1 Incidence of fever on each posttreatment day (the drugs were administered on day 1)

considered to represent neutropenic or infection-based fevers. Fevers occurred on posttreatment days 3 and 4 in 11 % of all cycles (113 of 1016) including 11 % (84 of 748) of the cycles involving males and 11 % (29 of 268) of those involving females. There was no significant difference in the percentage of cycles in which fevers occurred on posttreatment days 3 and 4 between the sexes ($p = 0.855$). The incidence of fever on posttreatment days 3 and 4 according to age was 12 % (≤60), 13 % (61–65), 10 % (66–70), 8 % (71–75), 13 % (76–80), and 10 % (≥81); this parameter did not differ significantly with age ($p = 0.427$). The incidence of fever on posttreatment days 3 and 4 according to the drugs administered (for the drugs that were used in ≥30 cases) is shown in Fig. 2. Gemcitabine was the drug that was most commonly associated with fever (20 %), followed by docetaxel (18 %), nedaplatin (12 %), and carboplatin (11 %). There was quite a large difference in the incidence of fever between the cases involving the top two drugs, gemcitabine and docetaxel, and those involving other drugs. In the incidence of fever on posttreatment day according to the drugs administered, many drugs including docetaxel and gemcitabine had fever distributions that peaked on posttreatment days 3 and 4 or later (figure not shown).

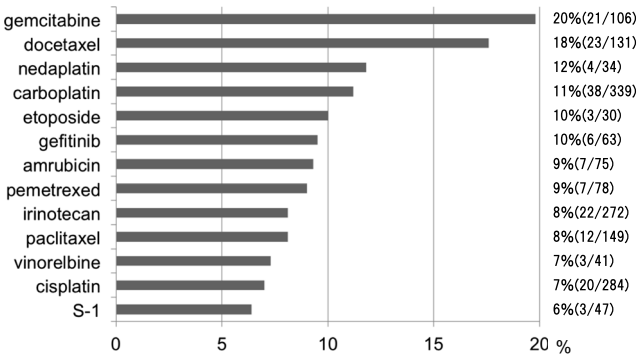

Fig. 2 Fever incidence on posttreatment days 3 and 4 according to the drugs administered

Causes of fever

The patients' fevers were caused by infections (47 %), adverse drug reactions (24 %), unknown causes (19 %), and tumors (7 %), as shown in Table 2. The causative infections included febrile neutropenia (50 %), pneumonia (18 %), unidentified infections (9 %), and colitis (7 %), as shown in Table 3. Central venous line infection based on culture was observed in one case. The correlation between the frequencies of radiotherapy and fever is shown in Table 4. The incidence of fever was significantly higher among the patients treated with radiotherapy than among those who did not receive radiotherapy (46 vs. 34 %, $p = 0.001$).

Use of G-CSF

The use of G-CSF was analyzed in 909 patients. Three hundred and three patients (33 %) received G-CSF and the remaining 606 patients (67 %) did not. The median and most common duration of G-CSF use was 3 days and ranges 1 to 15 days. Each incidence ratios of fever in G-CSF use duration were as follows: 22 % (8/37) in 1, 35 % (17/48) in 2, 33 % (27/81) in 3, 49 % (17/35) in 4, 73 % (24/33) in 5, 40 % (10/25) in 6, 56 % (9/16) in 7, 63 % (5/8) in 8, 71 % (5/7) in 9, 75 % (3/4) in 10, 100 % (3/3) in 11, 100 % (4/4) in 12, 100 % (1/1) in 13, and 100 % (1/1) in 15 days. Totally, the incidence ratios of fever in patients who received G-CSF and did not receive G-CSF were 44 % (134/303) and 31 % (188/606), respectively, which are significantly different ($p < 0.001$).

Discussion

Fevers of ≥37.5 °C during cancer chemotherapy occurred in 36 % of cycles, and the causes of these febrile episodes included infection, drug fever, unknown causes, and tumors. Overall, the incidence of fever increased until day 12 and then gradually fell. This pattern was considered to represent the

Table 2 Causes of fever

	Number of samples	Percentage
Infection	174	47.4
Drug-induced	88	24.0
Unknown	68	18.5
Tumor	27	7.4
Pleurodesis	5	1.4
Ileus	2	0.5
Others	3	0.8

Others included cerebral infarction, multiple compression fractures, and postoperative fever due to uterine scraping

Table 3 Causes of infection-derived fever

	Number of samples	Percentage
Febrile neutropenia	87	50.0
Pneumonia	31	17.8
Unidentified infection	15	8.6
Colitis	12	6.9
Influenza	6	3.4
Urinary tract infection	6	3.4
Sepsis	4	2.3
Respiratory tract infection	4	2.3
Pancreatitis	2	1.7
Arthritis	2	1.7
Others	5	2.9

incidence of fever caused by neutropenia or other myelotoxicity-associated infections. However, a second peak in the incidence of fever occurred on posttreatment days 3 and 4 and was considered to be due to drug fever because chemotherapy-associated myelotoxicity is not usually observed in this period.

Drug fever is defined as "a disorder characterized by fever coinciding with the administration of a drug and disappearing after the discontinuation of the drug, when no other cause for the fever is evident after a careful physical examination and laboratory investigation" [6]. We carefully examined the cause of fever in each case. Anticancer agents were usually administered on day 1 in the absence of fever, before being discontinued on day 2. In the cases in which fever developed on days 3 and 4 and then disappeared on days 4 and 5, and in which other causes of fever had been ruled out after a careful investigation, we finally decided that the fever had been caused by an adverse drug reaction. Research into fever after cancer chemotherapy has focused on febrile neutropenia and infection-derived fevers [1–3, 9–11]; therefore, the finding that drug fever is quite common after chemotherapy will aid the management of chemotherapy. Antibacterial and antifungal prophylaxes are only recommended for patients expected to have <100 neutrophils/μL for >7 days [12]. While physicians and medical staff are nervous about fevers that develop during cancer chemotherapy, they should take a wait-and-see approach or only treat the patient's symptoms if they suspect drug fever on posttreatment days 3 and 4. In addition, in such cases there is no need to produce blood cultures (to detect sepsis), collect blood for hematological or biochemical examinations (to search for a fever focus), perform urinary sediment examinations (to search for urinary infections), or administer preventive antibiotic therapy. Regarding chemotherapy cycles, fever was observed commonly in the first cycles (41 %) and caused a gradual decline. There was a significant difference in fever frequency between the first and subsequent cycles of therapy. One obvious reason is that physicians reduce the dose of anticancer agents in the next cycles when febrile neutropenia occurs. In our analysis of the effects of each drug, gemcitabine and docetaxel were the drugs that were most frequently associated with drug fever. Although most of the febrile episodes caused by these drugs occurred on posttreatment days 3 and 4, the incidence of gemcitabine-induced fever peaked on posttreatment day 3 (followed by day 4) whereas that of docetaxel-induced fever peaked on day 4 (followed by day 3). The incidence of fever also peaked on posttreatment days 3 and 4 in the patients treated with carboplatin or other drugs. Overall, the incidence of febrile episodes was highest on posttreatment day 4, followed by day 3, and then day 12. It is interesting that the incidence of the fevers induced by the abovementioned anticancer drugs did not peak on days 1 and 2. This delay was considered to have been due to the time required for a physical reaction to the drugs to develop and might have been affected by the use of dexamethasone as an antiemetic on day 1.

We also analyzed whether radiotherapy increases the frequency of fever, as fever is a known complication of radiotherapy [13, 14]. The frequency of fever was 34 % among the patients who received chemotherapy alone and significantly increased to 46 % among the patients who received both chemotherapy and radiotherapy. The present findings demonstrate that radiotherapy induces fever as a result of the body's reaction to radiation. In our analysis of the effects of age on the incidence of fever, although age was not found to be significantly associated with the incidence of fever, the frequency of fever fell in the 61–75-year-old age group, but then increased in the 76–80-year-old age group, before decreasing again in the 80-year-old age group. As elderly patients usually exhibit fewer biological responses such as fever [15], the peak in the 76–80-year-old age group seems strange. One possible reason is that cisplatin is used less frequently to treat patients who are ≥75 years old because of its non-hematological toxicities, which include nausea, vomiting, fatigue, and appetite loss, and the fact that its administration requires the infusion of a greater amount of solution due to renal toxicity. However, of

Table 4 Influence of radiotherapy on fever

	Fever		Total	Percentage	*p*
	(+)	(−)			
RT (+)	90	104	194	46.4	0.001
RT (−)	277	545	822	33.7	–

RT radiotherapy

the anticancer drugs examined in the present study, cisplatin was associated with the lowest incidence of fever on days 3 and 4, which might have been partially due to the fact that its administration involved greater amounts of dexamethasone and infusion solution than the administration of other agents. Secondly, elderly patients suffer more complications including infections [16] before chemotherapy and so are more likely to develop fever. Furthermore, a poor fever response in elderly patients has been suggested to make the diagnosis of infection and sepsis more difficult [16], and advancing age was reported to be significantly associated with more serious disease and chemotherapy discontinuation among patients with febrile illnesses [17, 18]. Thus, it might be appropriate to focus on preventing fever in elderly patients receiving cancer chemotherapy. In an analysis of the effects of sex, the males tended to exhibit a higher incidence of fever, but the difference was not significant. There was also no difference in the frequency of fever on posttreatment days 3 and 4 between the sexes. Thus, the incidence of fever during cancer chemotherapy is considered to be similar in both sexes. The use of G-CSF in our study is an important issue to discuss. Based on our data, the drugs were normally used when patients experienced grade 4 neutropenia with the intent of decreasing the incidence of febrile neutropenia or improving quality of life. Median duration of use was 3 days, and the incidence ratios of fever in patients who received G-CSF were significantly higher than those who did not receive G-CSF (44 vs. 31 %, $p < 0.001$). Although G-CSF use might contribute to the development of fever, we are unable to make this determination as it is extremely difficult to differentiate between fever caused by G-CSF and neutropenia.

In conclusion, our retrospective analysis of consecutive patients who were treated with chemotherapy demonstrated that episodes of fever that occur on posttreatment days are affected by drug fever on days 3 and 4. Knowledge of this pattern should help to prevent unnecessary examinations and treatments including prescribing antibiotics.

Conflict of interest The authors declare that they have no competing interests.

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