Interstitial pneumonia in patients receiving granulocyte colony-stimulating factor during chemotherapy: survey in Japan 1991–96

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Summary Twenty cases of interstitial pneumonia secondary to treatment with granulocyte colony-stimulating factor (G-CSF) were reviewed. Their interstitial pneumonia had the following features: (a) it occurred predominantly in patients aged 60 years or older; (b) it was prevalent among patients with haematological malignancies, particularly non-Hodgkin's lymphoma; (c) in all patients G-CSF was given after anti-cancer agents with potential to affect the lungs; (d) at the onset, many patients had symptoms such as dyspnoea and fever; and (e) the leucocyte (neutrophil) count as well as lactate dehydrogenase (LDH) and C-reactive protein (CRP) levels were usually higher than normal at the onset. These findings indicate that, when G-CSF is used in combination with pneumotoxic anti-cancer agents, respiratory function should be monitored before and during treatment. If the leucocyte (or neutrophil) count and/or LDH and CRP increase suddenly in association with dyspnoea and fever during administration of G-CSF, interstitial pneumonia should be suspected. Accordingly, a chest radiograph and pulmonary functional tests should be performed promptly. If a diagnosis of interstitial pneumonia is made, steroid pulse therapy should be commenced immediately.

Keywords: granulocyte colony-stimulating factor; interstitial pneumonia; haematological malignancy

Granulocyte colony-stimulating factor (G-CSF) is used to treat granulocytopenia secondary to cancer chemotherapy and bone marrow transplantation. It is effective in reducing the occurrence of fever and infection associated with granulocytopenia. Although the well-known adverse events of G-CSF are fever, bone pain and liver dysfunction, these problems are largely transient and disappear after the completion of treatment (Niitsu and Umeda, 1994). Recently, compared with many other countries, interstitial pneumonia possibly related to G-CSF administration appears to be more frequently observed in Japan (Iki et al, 1993; Katoh et al, 1993; Okubo and Nakazawa 1993; Murayama et al, 1994), although the link between pneumonitis and G-CSF has not been clearly explained. GM-CSF, another haematopoietic growth factor, has been associated with adult respiratory distress syndrome (ARDS) and acute respiratory insufficiency (Wiley et al, 1993). Precise knowledge of the characteristics of interstitial pneumonia due to G-CSF is necessary for early diagnosis and this may allow us to improve the treatment. Accordingly, we reviewed cases of interstitial pneumonia secondary to G-CSF therapy reported in Japan to clarify its clinical characteristics as well as possible methods of diagnosis and treatment.

MATERIALS AND METHODS

The subjects of this study were patients receiving either filgrastim or lenograstim and who presented symptoms consistent with the diagnosis for interstitial pneumonia between November 1991 and January 1996 by the criteria shown below. The criteria for diagnosis of interstitial pneumonia were determined as follows: (a) chest radiograph films and computerized tomography (CT) scans that showed findings characteristic of interstitial pneumonia; (b) the PaO2 was ≤ 70 mmHg at onset or decreased by 20 mmHg after administration of G-CSF; (c) infection and tumour metastasis were excluded by bacteriological, cytological and histological examination of sputum, bronchoalveolar lavage fluid and transbronchial biopsy specimens that were used to detect bacteria, fungi, protozoa and viruses or because neither organisms nor tumour cells were detected in any of these specimens; and (d) interstitial pneumonia developed within 10 days of completion of G-CSF therapy after administration of anti-cancer agents. Patients with a history of lung disease were not included in this study. Twenty patients were diagnosed with interstitial pneumonia using the above criteria and all of them were reported to the Japanese Ministry of Health and Welfare.

RESULTS

Background data on patients

The 20 patients with concurrent interstitial pneumonia were aged 63 years on average and 14 were at least 60 years old, indicating that it predominantly affected elderly patients. The primary
Table 1 Characteristics of patients who developed interstitial pneumonia during treatment with recombinant human granulocyte colony-stimulating factor

| Characteristics                  | Number of patients | Median age (range) years | Sex: male/female |
|----------------------------------|--------------------|--------------------------|------------------|
| Non-Hodgkin’s lymphoma           | 19                 | 63 (41–73)               | 10/10            |
| Phenotype                        | Low grade          | 1                        |                  |
|                                  | Mixed              | 10                       |                  |
|                                  | Diffuse small cleaved | 1                       |                  |
| High grade                       | 1                  |                          |                  |

*French–American–British classification.

disease was haematological malignancy in all 20 patients. Nineteen of them had non-Hodgkin’s lymphoma (NHL) and one had acute monocytic leukaemia (M5b: French–American–British classification). NHL was of intermediate grade in 89.5% and mainly in the advanced stages according to the Ann Arbor classification (Table 1). On admission, none of the patients showed any significant changes in peripheral blood findings, pulmonary function, immunology or coagulation parameters (Table 2).

**Association of interstitial pneumonia with chemotherapy regimens, number of chemotherapy courses and response to treatment (Table 3)**

All 20 patients received G-CSF as adjuvant therapy during cancer chemotherapy.

The chemotherapy regimens used always included pneumotoxic agents, such as cyclophosphamide (CPA), bleomycin (BLM), methotrexate (MTX) and etoposide (VP-16). Interstitial pneumonia developed most commonly (in seven patients) during the second course of chemotherapy and in 15 patients before the fourth course of chemotherapy. The median total doses of pneumotoxic chemotherapy agents were CPA 1800 mg m⁻² (584–5250), BLM 18 mg m⁻² (11–55), MTX 1137 mg m⁻² (321–3094), VP-16 394 mg m⁻² (345–1859) and the numbers of treated patients were 19 (95%), 11 (55%), 5 (25%), and 4 (20%).

Table 2 Comparisons of laboratory findings between baseline and at onset of interstitial pneumonia during treatment with recombinant human granulocyte colony-stimulating factor

|                                | Baseline          | At onset of interstitial pneumonia |
|--------------------------------|-------------------|------------------------------------|
| Haematological examinations    |                   |                                    |
| WBC (μl)                       | 5100 (1700–11300) | 10000 (3800–41500)                |
| Neutrophil (μl)                | 2438 (816–6995)   | 8000 (2700–20925)                 |
| Platelet (x 10⁹ μl⁻¹)          | 23.8 (2–48)       | 18.5 (9.9–162)                    |
| RBC (x 10⁹ μl⁻¹)               | 429.5 (302–470)   | 332 (13.4–448)                    |
| Haemoglobin (g dl⁻¹)           | 12.4 (8–14)       | 10.4 (7–13)                       |
| LDH (IU l⁻¹)                   | 331 (212–646)     | 607 (248–1072)                    |
| CRP (mg dl⁻¹)                  | 0.3 (0–3.44)      | 3.2 (0–26.2)                      |
| Immunological examinations     |                   |                                    |
| IgG (mg dl⁻¹)                  | 291 (191–438)     | 186 (129–371)                     |
| IgM (mg dl⁻¹)                  | 1841 (1460–5174)  | 1620 (591–2090)                   |
| T cell (%)                     | 171 (84–722)      | 124 (50–268)                      |
| B cell (%)                     | 92 (82.1–98)      | 92 (87–98)                        |
| CD4 (%)                        | 28.6 (27.2–48.3)  | 30.1 (28.6–34.5)                  |
| CD8 (%)                        | 21.4 (7.6–48.4)   | 25.9 (14.9–38.1)                  |
| CD4/CD8 ratio                  | 1.41 (0.68–6.36)  | 1.32 (0.85–2.01)                  |
| Pulmonary function test        |                   |                                    |
| PaO₂ (kPa)                     | 11.5 (10.0–13.4)  | 7.0 (4.3–9.7)                     |
| PaCO₂ (kPa)                    | 5.3 (4.6–5.5)     | 4.5 (3.6–6.1)                     |
| AaDO₂ (kPa)                    | 2.0 (0.1–4.4)     | 7.4 (3.0–10.4)                    |
| %DICO₂                        | 93 (82–98)        |                                    |
| Coagulation test               |                   |                                    |
| PT (second)                    | 11.4 (10.0–11.9)  | 11.4 (10.1–11.8)                  |
| APTT (second)                  | 33.4 (26.2–43.6)  | 36.0 (27.4–43)                    |
| FDP (μg ml⁻¹)                  | ≤10               | ≤10                                 |
| Fibrinogen (mg dl⁻¹)           | 384 (126–561)     | 403 (145–555)                     |
| D-dimer (ng ml⁻¹)              | ≤100              | ≤100                                |

Values are given as median (range). *During chemotherapy before G-CSF administration and before onset of interstitial pneumonia episode. Abbreviations: WBC, white blood cell; RBC, red blood cell; PaO₂, partial pressure of arterial oxygen; PaCO₂, partial pressure of arterial carbon dioxide; AaDO₂, arterial–alveolar difference of oxygen; DLCO, pulmonary diffusing capacity for carbon monoxide; PT, prothrombin time; APTT, activated partial thromboplastin time; FDP, fibrinogen degradation products.
### Table 3  
Chemotherapy regimens, clinical response and total dose of anti-cancer agents and G-CSF until onset of interstitial pneumonia in the 20 patients

| Number | Sex | Age | Diagnosis      | Chemotherapy regimen | Course at onset | Clinical response | CPA (mg m⁻²) | BLM (mg m⁻²) | MTX (mg m⁻²) | VP-16 (mg m⁻²) | G-CSFb | Durations (day) |
|--------|-----|-----|----------------|----------------------|-----------------|------------------|--------------|--------------|--------------|---------------|--------|-----------------|
| 1      | M   | 41  | NHL            | Pro-MACE             | 2               | CR               | 2652         | 3094         | 442          | 1650          | 1650  | 12              |
| 2      | M   | 56  | NHL            | COP-BLAM III        | 1               | PR               | 782          | 28           | 600          | 4             | 600    | 4               |
| 3      | F   | 63  | NHL            | COP-P/CHOP          | 2               | PR               | 1242         |              | 375          | 5             |        |                 |
| 4      | F   | 65  | NHL            | COP-BLAM III        | 4               | CR               | 1655         | 29           | 750          | 10            |        |                 |
| 5      | F   | 62  | NHL            | COP-BLAM III        | 7               | CR               | 1972         | 55           | 450          | 6             |        |                 |
| 6      | F   | 66  | NHL            | COP-BLAM            | 2               | CR               | 584          | 15           | 300          | 4             |        |                 |
| 7      | M   | 73  | AmoL           | AraC + VP-16        | 4               | PR               |              | 1859         | 1280         | 8             |        |                 |
| 8      | M   | 71  | NHL            | ProMACE-CytobOM     | 4               | CR               | 1728         | 14           | 321          | 346           | 450    | 19              |
| 9      | F   | 68  | NHL            | CHOP                | 4               | PR               | 2786         |              | 1790         | 19            |        |                 |
| 10     | F   | 66  | NHL            | CHOP                | 2               | CR               | 800          |              | 570          | 5             |        |                 |
| 11     | F   | 47  | NHL            | CHOP                | 4               | CR               | 4000         |              | 400          | 4             |        |                 |
| 12     | M   | 69  | NHL            | CHOP                | 2               | PD               | 706          |              | 700          | 7             |        |                 |
| 13     | F   | 64  | NHL            | DXR+VP-16+CPA+VCR+BLM+PSL | 6               | CR               | 3500         | 17           | 345          | 345           | 500    | 5               |
| 14     | F   | 55  | NHL            | COP-BLAM            | 2               | CR               | 1200         | 15           | 600          | 6             |        |                 |
| 15     | M   | 48  | NHL            | COP-BLAM            | 3               | PR               | 1800         | 11           | 700          | 6             |        |                 |
| 16     | F   | 63  | NHL            | COP-BLAM            | 3               | CR               | 1800         | 21           | 600          | 6             |        |                 |
| 17     | M   | 49  | NHL            | MACOP-B             | 12 weeks        | Unknown          | 2160         | 30           | 1240         | 600           | 5      |                 |
| 18     | M   | 62  | NHL            | MACOP-B             | 11 weeks        | Unknown          | 1989         | 18           | 1137         | 1750          | 14     |                 |
| 19     | M   | 62  | NHL            | CHOP                | 7               | CR               | 5250         |              | 1100         | 12            |        |                 |
| 20     | M   | 67  | NHL            | CHOP                | 2               | CR               | 1500         |              | 1100         | 12            |        |                 |

*Total dose administered until onset of interstitial pneumonia episode.  
Total dose administered only course at onset of interstitial pneumonia episode.  
Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; COPP, cyclophosphamide, vincristine, procarbazine, prednisolone; ProMACE-CytobOM, prednisolone, methotrexate, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine; COP-BLAM, COP-BLAMIII, cyclophosphamide, vincristine, prednisolone, bleomycin, doxorubicin, procarbazine; MACOP-B, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisolone, bleomycin; CR, complete remission; PR, partial remission; PD, progressive disease.

**Imaging findings**

The most common finding on chest radiograph films was a granular or reticular pattern throughout the lung fields, which was observed in 12 patients, followed by a similar pattern involving the lower fields of both lungs. CT scans of the chest showed a granular or reticular pattern extending throughout both lungs in 77.8% of patients.

**Findings on bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB)**

BAL was performed in seven patients and the total cell count of all patients excluding one patient was measured. It was unmeasurable in one patient. The total cell count increased in all six patients. The percentage of lymphocytes and neutrophils increased in four and two patients respectively. The CD4/CD8 ratio decreased in five patients and it was less than 1. TBLB performed in three patients shows typical histological changes of interstitial pneumonia. Figure 1A and B shows the changes in the same patient and Figure 1C shows the changes in another patient. These figure of typical histological changes are similar to interstitial pneumonia, with the apparent thickening of alveolar walls and infiltration of small round cells. Also, a small amount of intra-alveolar exudative pneumonia was observed, as well as granuloma formation in two cases.

**Clinical characteristics at the onset of interstitial pneumonia (Tables 4, 5 and 6)**

**Symptoms**

The most common symptom of interstitial pneumonia was dyspnoea (11 patients, 55%) followed by fever (ten patients, 50%).

**Leucocyte and neutrophil counts and serum levels of LDH and CRP**

At the onset of interstitial pneumonia the leucocyte count was ≥10 000 μl⁻¹ in ten patients and the neutrophil count was ≥5000 μl⁻¹ in 11 patients. Interstitial pneumonia most frequently developed 6 days after the leucocyte (neutrophil) nadir or after rapid recovery of the leucocyte count. At the onset of interstitial pneumonia, lactate dehydrogenase (LDH) increased in 12 patients and C-reactive protein (CRP) increased in 14 patients.

**Treatment and outcome**

Of the 20 patients, 19 received steroid pulse therapy; the remaining patient received O₂ administration. A total of 17 patients who were treated in the earliest part of the study period recovered, but three patients in this group eventually died because of respiratory insufficiency and multiple organ failure.
**DISCUSSION**

G-CSF has been used to treat various forms of neutropenia. This drug is believed to increase the neutrophil count and enhance neutrophil function (Pettengell et al, 1992). The activation of neutrophils is called a priming effect by which G-CSF enhances neutrophil phagocytosis and migration as well as superoxide production (Laver and Moore, 1989). These are important biological defence mechanisms that primarily act to prevent bacterial invasion but simultaneously enhance inflammatory reactions that can injure host tissues (Weiland et al, 1986). It has been reported that neutrophils are involved in the progression of ARDS. In BAL fluid from patients with ARDS, neutrophils are increased in number and there is an increase in neutrophil elastase activity (Idell et al, 1985). In BAL fluid from patients with interstitial pneumonia, the G-CSF production by alveolar macrophages is increased significantly, suggesting involvement of G-CSF in the pathogenesis of this condition (Tazi et al, 1991).

Interstitial pneumonia related to the use of G-CSF has occasionally been reported and many mechanisms have been proposed for its aetiology. Matthews (1993) suggested that G-CSF might augment the pneumotropic toxicity of BLM because pneumotoxicity occurred in three out of five patients with NHL who received ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) plus G-CSF. Dirix et al (1994) considered that BLM pneumonia might be made worse by a rapid increase in the number and activity of neutrophils because of G-CSF. BLM is thought to react with Fe$^{2+}$ to produce superoxide (O$_2^-$), which damages DNA molecules and gives rise to pulmonary dysfunction (Sausville et al, 1978). According to Bastion et al (1994), who conducted two randomized placebo-controlled trials in NHL patients to assess the effectiveness of G-CSF, chemotherapy including BLM given in combination with G-CSF did not augment the pneumotropic toxicity of bleomycin. Another clinical study assessed pulmonary disease in patients with aggressive NHL who received BACOP (bleomycin, doxorubicin, cyclophosphamide, vincristine, prednisolone) therapy with or without G-CSF. Pneumonia occurred in 33% of patients receiving BACOP with G-CSF and in 4% of the control patients. The authors recommended that G-CSF should be used carefully when combined with chemotherapy regimens that involve repeated BLM administration over a long period (Lei et al, 1994). The mechanism by which G-CSF when combined with certain anti-cancer agents gives rise to pneumonia remains to be clarified. G-CSF has not been reported to cause pneumonia in patients receiving it alone and it only causes pneumonia in patients receiving combined therapy with anti-cancer agents. This suggests that G-CSF increases the number of activated neutrophils that exert a deleterious effects on subclinical lung damage produced by anti-cancer agents and results in the manifestation of pulmonary dysfunction.

In addition to the effect on haemopoiesis, G-CSF enhances mature neutrophil functions both in vitro and in vivo. Previous studies indicated that G-CSF administration enhances superoxide release in neutrophils from patients with malignant lymphoma (Ohsaka et al, 1989). And Ohsaka et al (1993) reported that G-CSF inversely regulates the surface expression of cellular adhesion molecules on human neutrophils, that is G-CSF down-regulates the expression of t-selectin and up-regulates the expression of CD11b/CD18 leucocyte integrin on neutrophils. These findings suggest that G-CSF may enhance host defence and participate in the inflammatory process through the neutrophil–endothelial cell interactions. However, neutrophil-derived oxygen metabolites and proteinases have also been implicated in the pathogenesis of tissue...
patients with haematological malignancies, particularly NHL; (c) all patients received G-CSF after administration of BLM, MTX, CPA, VP-16 or other pneumotoxic anti-cancer agents; (d) the onset of interstitial pneumonia occurred during administration of G-CSF in 12 out of 20 patients; (e) the earliest symptoms of interstitial pneumonia were usually dyspnoea and a temperature ≥ 38°C; (f) the onset was associated with an increase in the leucocyte (neutrophil) count in many cases; (g) initial elevation of the LDH and CRP levels was observed in 12 and 14 patients respectively; (h) on chest radiograph films, changes appeared first in the lower lung fields and spread gradually over the entire lungs; (i) in many patients, the total cell count in BAL fluid was increased; and (j) alleviation of interstitial pneumonia was achieved in patients treated by steroid pulse therapy soon after onset. In brief, when G-CSF is given to patients who have previously received pneumotoxic anti-cancer agents, such as bleomycin and methotrexate, pulmonary function should be monitored by measuring PaO₂ and %DLCO before and during G-CSF therapy. Interstitial pneumonia should be suspected if dyspnoea and fever are associated with rapidly increasing leucocyte and neutrophil counts, as well as an elevation of LDH and CRP during administration of G-CSF. The diagnosis should be confirmed by pulmonary function tests and chest radiograph examination. It is important to start steroid pulse therapy as early as possible when the diagnosis is made.

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