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Impact of severe acute respiratory syndrome on the status of lung cancer chemotherapy patients and a correlation of the signs and symptoms

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Summary Our aim was to describe the impact of severe acute respiratory syndrome (SARS) on the status and chemotherapy of non-small-cell lung cancer (NSCLC) patients who had entered clinical trials, and to review how to differentiate the signs and symptoms of SARS from lung cancer and its treatment-related toxicities. A prospective case series involving 79 NSCLC patients who were enrolled in clinical trials undergoing chemotherapy at Taipei Veterans General Hospital, between April 1 and July 15, 2003, was studied. Whether or not there existed a delay, omission, or refusal of scheduled chemotherapy, was recorded. Whether or not our patients had been suspected of or treated as having SARS, was recorded. The patients filled out questionnaires regarding lung cancer treatment and the risk of getting SARS from the hospital. Among these patients, five were placed in an isolation unit to rule out SARS infection during this period of time, and no patient was documented to have suffered from a SARS infection after examinations. Of 373 scheduled chemotherapy injections in 79 patients, a delay in treatment occurred only 10 times. Three patients refused further chemotherapy because of a fear of getting SARS if they visited the hospital. Fifty-eight patients responded to our questionnaires. Thirty-seven patients (63.8%) were afraid of visiting hospital during this SARS infection period. Twenty-one patients (36.2%) felt that a SARS infection was more severe and fatal than their lung cancer. In conclusion, SARS is a new disease entity that is highly contagious. Its clinical manifestations overlap with the signs and symptoms of lung cancer. Thus, a clear differentiation between the two conditions is needed, especially for those patients who are under active anti-cancer treatment.

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1. Introduction

Severe acute respiratory syndrome (SARS) is a new infectious disease in humans, first recognized in late February 2003, in Hanoi, Vietnam [1]. Later, investigators found that SARS had first manifested in humans in Guangdong province in China, and
subsequently spread worldwide [2]. A new coronavirus was identified as the causative agent of SARS. Taiwan was also affected by SARS from the end of February 2003, and the situation began worsening in April 2003 [3]. The majority of cases in the SARS outbreak in Taiwan were related to hospital exposure.

As defined by the WHD, a suspected case of SARS is an individual with fever (temperature >38°C), cough, or dyspnea, and contact with an individual believed to have SARS, who has traveled to an area with recent local transmission of the disease, or who resides in an area with recent local transmission of SARS. A probable case is an individual meeting criteria for a suspected case along with radiographic features of pneumonia or respiratory distress syndrome, showing positive for SARS coronavirus in one or more assays, or having an unexplained respiratory illness resulting in death, with autopsy results demonstrating the pathology of respiratory distress syndrome without an identifiable cause [2]. As of August 7, 2003, probable SARS cases had been reported in 30 countries (32 areas), involving 8422 individuals, and causing 916 deaths [4]. Taiwan was the third most severely infected area, following China and Hong Kong.

Lung cancer patients frequently have pulmonary symptoms, such as cough and dyspnea. They easily suffer from fever, either due to infection, drug-induced causes, radiation, chemotherapy-induced febrile neutropenia, or tumor fever. Because of existing chest roentgenographic abnormalities and pulmonary symptoms, they are easily misdiagnosed as SARS patients, especially when fever occurs.

Taipei Veterans General Hospital is the leading center for chemotherapy clinical trials for lung cancer in Taiwan. It was also an important anti-SARS medical center during the SARS outbreak period in Taiwan. In this paper, we describe the experience of the impact of the SARS outbreak upon non-small-cell lung cancer (NSCLC) patients undergoing chemotherapy clinical trials in our hospital. As lung cancer patients have many clinical signs and symptoms similar to SARS patients, our experience may benefit others who may deal with lung cancer patients and a possible SARS outbreak in the near future.

2. Patients and methods

We prospectively followed our NSCLC patients who were enrolled in clinical trials undergoing chemotherapy at Taipei Veterans General Hospital, Taiwan, between April 1 and July 15, 2003. Whether or not there existed a delay, omission, or refusal of scheduled chemotherapy was recorded and the causes analyzed. Whether or not patients had been suspected of or treated as having SARS, or quarantined due to possible contact with SARS patients, was also recorded and the causes reviewed. The patients filled in questionnaires regarding the importance of lung cancer treatment and the risk of getting SARS during travel to or while staying in the hospital.

3. Results

Seventy-nine NSCLC patients were participating in our chemotherapy clinical trials between April 1 and July 15, 2003. Among them, five patients had been placed in our isolation unit to rule out SARS infection during this period, because they had exhibited clinical pictures similar to SARS infection or had a contact history with a SARS patient (Table 1). All five patients had a negative coronavirus study.

| Table 1 | Demographic data of five NSCLC patients who had been suspected of having SARS and were isolated |
|---------|-------------------------------------------------------------------------------------------------|
| Underlying condition | Presenting symptoms | Treatment | Outcome |
| Docetaxel-induced interstitial pneumonitis | Progressive dyspnea, followed by mild fever after two cycles of treatment | Corticosteroid | Recovered |
| Lymphangitis carcinomatosis | Progressive dyspnea and mild fever | Corticosteroid, antibiotics | Died 7 days later |
| Febrile neutropenia | Fever 7 days after chemotherapy | Antibiotics | Recovered |
| Post-obstructive pneumonitis | Productive cough, followed by fever | Antibiotics | Recovered |
| Hypoglycemia | Loss of consciousness | Intravenous dextrose infusion | Recovered |

*All five patients had chest X-ray findings that were not easy to differentiate from SARS.

*These two patients had been staying in the same room with a probable SARS patient for 2 days and 1 day, respectively.*
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Table 2

| Item                                                                 | Patient number (%) |
|----------------------------------------------------------------------|--------------------|
| Did you know about the SARS outbreak in Taiwan?                      | 58 (100) 0         |
| Were you afraid to visit any hospital?                               | 37 (63.8) 21 (36.2) |
| Will you refuse to receive chemotherapy in our hospital if a SARS outbreak occurs here? | 29 (50) 29 (50) |
| Did you lose confidence in Taiwan’s hospitals?                       | 16 (27.6) 42 (72.4) |
| Did you feel that SARS was more severe and fatal than lung cancer?   | 21 (36.2) 37 (63.8) |
| Did you worry your cancer condition would get worse due to the SARS outbreak? | 46 (79.3) 12 (20.7) |

Of 373 scheduled chemotherapy injections for 79 patients, either in the outpatient clinic or under hospitalization, a delay in treatment occurred only 10 times. Three patients refused further chemotherapy because of a fear of getting SARS if they visited the hospital. Fifty-eight patients responded to our questionnaires. They all knew that a SARS outbreak had occurred in Taiwan, 63.8% of patients were afraid of visiting any hospital during this period, and 36.2% felt that the SARS infection was more severe and fatal than their lung cancer. The details are shown in Table 2.

4. Discussion

In Canada’s experience, SARS had spread to other patients and health care workers within the Toronto hospital prior to a significant awareness of SARS by the medical community. Other hospitals in Toronto were affected when patients were transferred between institutions [5]. The same situation occurred in Taiwan [2]. Thus, many patients were afraid to visit the hospital during the SARS infection period, due to a fear of being infected.

The earliest symptoms of SARS during the outbreak usually included fever or prodromal symptoms [5], and the common clinical features at the time of admission were fever (99—100%), followed by nonproductive cough, myalgia, and dyspnea [5,6]. Unilateral and bilateral pulmonary infiltrates on chest radiography at admission were observed in 46% and 29% of SARS patients, respectively [5]. The differential diagnosis of pulmonary infiltrates is extensive in lung cancer patients with fever, including bacterial infection, opportunistic infection, pulmonary hemorrhage, lymphangitic carcinomatosis, pulmonary embolism, pulmonary edema, chemotherapy and/or radiotherapy-induced lung injury, and leukoagglutinin transfusion reactions [7]. It is difficult to use the chest roentgenogram alone for the differential diagnosis of lung cancer with or without SARS infection. Among the diagnoses that require differentiation, chemotherapy-induced febrile neutropenia, chemotherapy-induced interstitial pneumonitis, radiation pneumonitis, and obstructive pneumonitis, were most commonly encountered (Table 3).

The patient’s clinical history (treatment-related or SARS contact history), the temporal relationship between the different signs and symptoms, laboratory data, and image findings are all needed for the differential diagnosis (Table 3) [8—12].

Despite the fact that 63.8% of our patients said that they were afraid of visiting the hospital during the SARS infection period, the majority of the patients received chemotherapy on time because they also feared that their lung cancer condition would worsen if they delayed treatment. More importantly, none of our patients were infected with SARS during this SARS outbreak period, despite their frequent hospital visits.

In conclusion, when dealing with lung cancer patients receiving chemotherapy during a SARS epidemic, we suggest considering less myelosuppressive chemotherapy regimens. Consideration should be given to outpatient clinical treatment instead of hospitalization, changing the weekly treatment to treatment every 3 or 4 weeks, and changing from intravenous chemotherapy to an oral form of treatment, to avoid frequent hospital visits. Routine use of influenza vaccine is also recommended for these immunocompromised cancer patients as a way to help the patients and avoid the need to differentiate between a diagnosis of SARS and influenza infection. Patients should always bring a brief medical summary with the diagnosis, the treatment given, and the date of treatment; to avoid being mistaken as a SARS patient. Furthermore, in the future, other new, as yet undiscovered, respiratory pathogens that may cause problems similar to or worse than SARS, and the lessons learned from
| Disease                        | History (Hx)     | Symptom/sign | Laboratory data                          | Image study                               |
|-------------------------------|------------------|--------------|------------------------------------------|-------------------------------------------|
| SARS                          | SARS contact Hx (+) | Fever preceding cough and dyspnea | Lymphopenia, LDH ↑, coronavirus (+)       | Uni- or bilateral infiltrates, usually multi-focal, mainly in the peripheral region and lower lobes |
| Febrile neutropenia           | Chemotherapy Hx (+) | Mainly fever | Leukopenia, neutropenia                  | Usually no specific new lesion            |
| Drug-induced interstitial pneumonitis | Chemotherapy Hx (+) | Progressive dyspnea preceding fever | No specific data                          | Uni- or bilateral progressive interstitial infiltration or consolidation |
| Radiation pneumonitis         | 1–3 months after radiotherapy | Dyspnea and/or dry cough preceding fever | No specific data                          | Hazy shadow similar to radiation ports    |
| Obstructive pneumonitis       | Cough and/or hemoptysis | Cough preceding fever | Leukocytosis                             | Mass with peripheral consolidation or collapse |
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differentiation between SARS and lung cancer patients receiving chemotherapy could be applied to that situation.

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