Biomarkers for cancer-related fatigue and adverse reactions to chemotherapy in lung cancer patients

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Abstract. This study was conducted to investigate the biomarkers that appear to be correlated with cancer-related fatigue (CRF) and the adverse reactions (ADRs) to chemotherapy. A total of 100 lung cancer patients were selected and CRF prior to and following chemotherapy was evaluated. The plasma levels of tumor necrosis factor (TNF)-α and interleukin (IL)-1 and the level of 17-hydroxycorticosteroid (17-OHCS) in the urine were analyzed and correlated with CRF and the ADRs associated with chemotherapy. The incidence of CRF was found to be 88.0% and ADRs following chemotherapy occurred in 15.0% of the patients. An increase in the TNF-α and IL-1 levels was detected in patients with CRF. The level of 17-OHCS in the urine was found to be elevated in cases that experienced ADRs following chemotherapy. In conclusion, CRF is closely correlated with increased plasma levels of TNF-α and IL-1. Furthermore, an abnormally elevated 17-OHCS level in the urine may be an important indicator predicting ADR development following chemotherapy.

Introduction

Cancer-related fatigue (CRF) is a subjective sensation of exhaustion experienced by cancer patients. Unlike fatigue in healthy individuals, CRF is persistent and is not relieved through rest. CRF exerts a detrimental effect on the emotional, physical and mental status of the patients (1) and is commonly accompanied by sleep disorders, pain and depression (2-4). It was reported that CRF occurs in >60% of cancer patients (5). CRF may affect the patients' daily routine, thus exerting a significant negative effect on the quality of life (QOL). A number of studies demonstrated that CRF is closely correlated with tumor necrosis factor (TNF)-α, interleukin (IL)-1 and 17-hydroxyl corticosteroid (17-OHCS) levels (6-9). With the advances in cancer treatment, increasing attention is focused on the management of CRF. Therefore, a better understanding of CRF and the adverse reactions (ADRs) associated with chemotherapy is required. In this study, we investigated biomarkers that appear to be correlated with CRF and the ADRs to chemotherapy in lung cancer patients. By testing these biomarkers in future clinical practice, certain pharmacological or non-pharmacological interventions may be implemented to achieve personalized treatment and improve the QOL of the patients.

Patients and methods

Patients. In this study, we selected 100 pathologically diagnosed lung cancer patients who received treatment at the Affiliated Cancer Hospital of Shantou University Medical College between February, 2012 and March, 2014. Patients with certain diseases, such as cardiac, hepatic, splenic and endocrine disorders, were excluded. Of the 100 patients, 56 were male and 44 female. The median age of the patients was 51 years (range, 18-80 years). Tumor staging was based on the 7th edition of 2009 TNM classification in Lung Cancer (10). A total of 32 patients had stage II, 39 had stage III and 29 had stage IV disease. All the enrolled patients were diagnosed with non-small-cell lung cancer, according to the 2004 World Health Organization classification of lung tumors (11). All the patients were treated with docetaxel and cisplatin. The dose of chemotherapy was determined by the body surface area of the patients (docetaxel, 75 mg/m^2/day; and cisplatin, 75 mg/m^2 was administered on days 1-3 of each treatment cycle). The drugs were administered via an intravenous drip. A single course of treatment lasted for 21 days and all the patients received 4-6 courses of treatment.

This study's protocol received Ethics Approval by the Institutional Review Board of Shantou University Medical College and all the patients provided written informed consent prior to their inclusion in the study.

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Table I. Normal range of human plasma TNF-α, IL-1 and urine 17-OHCS levels.

Testing reagents	Gender	Normal range
Plasma TNF-α	Male and female	0.74-1.54 ng/ml
Plasma IL-1	Male and female	0.13-0.25 ng/ml
Urine 17-OHCS	Male	3-10 μg/l
	Female	2-8 μg/l

TNF-α, tumor necrosis factor-α; IL-1, interleukin 1; 17-OHCS, 17-hydroxycorticosteroid.

Reagents and testing methods. In this study, all the reagents were provided by Shanghai Yanjin Biological Co., Ltd., (Shanghai, China). The testing kits included human TNF-α, IL-1 and human urine 17-OHCS.

Samples of 3 ml peripheral venous blood and 5 ml urine were freshly collected on the day prior to and at 2 days following chemotherapy. The blood and urine samples were centrifuged at 3,000 rpm for 30 and 20 min, respectively. The supernatants were stored in -20˚C refrigerator until use. The ELISA method was applied to measure the plasma levels of TNF-α and IL-1 and the urine level of 17-OHCS, according to the manufacturer's instructions. The optical density (OD) values were measured at a wavelength of 450 nm. Using the standard concentration as the x-axis and the OD value as the y-axis, a standard linear regression curve was drawn in an Excel worksheet. The plasma levels of TNF-α and IL-1 and the level of 17-OHCS in the urine were calculated based on the linear regression curves.

Evaluation of CRF. Based on the Okuyama *et al* (12) scoring system, each lung cancer patient was evaluated on the day prior to and at 2 days following chemotherapy using the Cancer Fatigue Scale (9,12), which is a 15-item questionnaire consisting of three subscales, namely physical (items 1, 2, 3, 6, 9, 12, 15), affective (items 5, 8, 11, 14) and cognitive (items 4, 7, 10, 13) subscales. According to the Likert's 5-scoring system, for each item, 0 indicated no fatigue and 5 indicated the most severe fatigue. The sum of each item score was defined as the total score. The possible total score range was 0-60 (the higher the score, the more severe the fatigue).

Using the ELISA method, each patient's plasma level of TNF-α and IL-1 and urine level of 17-OHCS were measured. In addition, the chemotherapy-associated ADRs were recorded. According to the occurrence of ADRs, all the enrolled patients were divided into two groups, namely the ADR and the non-ADR groups. A comprehensive evaluation of a CRF-ADR scale was established and the correlation between lung cancer fatigue and chemotherapy-associated ADRs was investigated.

Statistical analysis. The CRF-ADR scale scores were expressed as means ± standard deviation. The Pearson's correlation coefficient was calculated using the SPSS software package, version 17.0 (SPSS, Inc., Chicago, IL, USA). $P<0.05$ was considered to indicate a statistically significant difference.

Results

CRFs and ADRs following chemotherapy. Of the 100 lung cancer patients, 88 (88%) had CRF prior to chemotherapy. The physical, affective and cognitive fatigue scores were 12.2±7.6, 6.2±4.3 and 26.4±14.9, respectively. A total of 15 patients (15%) experienced ADRs following chemotherapy (skin rash, 8 patients; dyspnea, 3 patients; and palpitations, 4 patients). These ADRs were treated with anti-anaphylactic drugs and oxygen inhalation. The majority of the ADRs developed 5-10 min following chemotherapy.

CRF and TNF-α, IL-1 and 17-OHCS levels. The normal range of plasma TNF-α and IL-1 and urine 17-OHCS levels is presented in Table I. The levels of plasma and urine markers are described as higher or lower than normal, if there are out of the normal range, as described in Table I.

TNF-α. Prior to chemotherapy, the average plasma TNF-α level was 2.0±0.6 ng/ml in the lung cancer patients, which was higher compared to the average of healthy individuals. A high level of plasma TNF-α was detected in 77 (77%) patients. Following chemotherapy, the average plasma TNF-α level increased further, reaching 2.4±0.6 ng/ml. A total of 81 patients (81%) exhibited higher plasma levels of TNF-α. Among these patients, 74 experienced fatigue prior to chemotherapy (84.1%, 74/88). The difference in increased TNF-α between patients who had fatigue prior to and those with fatigue after chemotherapy was statistically significant (P=0.022).

IL-1. Prior to chemotherapy, the average plasma IL-1 level was 0.3±0.1 ng/ml in this group of patients. A total of 68 patients (68%) exhibited higher levels of IL-1. Folowing chemotherapy, the average plasma IL-1 increased to 0.4±0.1 ng/ml, with 70 patients (70%) exhibiting higher plasma IL-1 levels. A total of 62 patients (70.5%, 62/88) experienced fatigue prior to chemotherapy. The difference in increased IL-1 between patients who had fatigue prior to and those with fatigue after chemotherapy was statistically significant (P=0.018).

17-OHCS. Prior to chemotherapy, the average urine 17-OHCS level was 6.1±2.4 ng/ml in this group of patients. A high level of urine 17-OHCS occurred in 7 patients (7%). Following chemotherapy, the average urine 17-OHCS level increased to 6.3±2.7 ng/ml, with 10 patients (10%) exhibiting higher levels, including 4 patients who already exhibited symptoms of fatigue prior to chemotherapy (4.5%, 4/88). The difference in increased 17-OHCS between patients who had fatigue prior to and those with fatigue after chemotherapy was not statistically significant (P=0.160).

Correlations of ADRs to chemotherapy with plasma TNF-α and IL-1 and urine 17-OHCS levels. In this study, a total of 81 patients exhibited abnormally increased plasma TNF-α levels following chemotherapy. Among these patients, only 5 experienced ADRs. Thus, the correlation between increased TNF-α levels and the occurrence of ADRs following chemotherapy was not statistically significant (33.3%, 5/15; P=0.250). Similarly, of the 70 patients who exhibited abnormally increased plasma IL-1 levels following chemotherapy,

Table II. Laboratory analysis and adverse reactions to chemotherapy.

Laboratory indicators	Cases with elevated laboratory indicators		Pre-chemotherapy fatigue			Post-chemotherapy adverse reactions		
	Cases	%	Cases	%	P-value	Cases	%	P-value
TNF-α	81	81.0	74	84.1	0.022	5	33.3	0.250
IL-1	70	70.0	62	70.5	0.018	5	33.3	0.109
17-OHCS	10	10.0	4	4.5	0.160	10	66.7	0.008

TNF-α, tumor necrosis factor-α; IL-1, interleukin 1; 17-OHCS, 17-hydroxycorticosteroid.

only 5 experienced ADRs. Thus, the correlation between increased IL-1 levels and the occurrence of ADRs following chemotherapy was also not statistically significant (33.3%, 5/15; P=0.109).

Of note, of the 15 patients who experienced ADRs following chemotherapy, 10 (66.7%) exhibited abnormally increased urine 17-OHCS levels. The correlation between increased 17-OHCS and the occurrence of ADRs to chemotherapy was statistically significant (P=0.008). The abovementioned results are summarized in Table II.

Discussion

A number of studies investigated the correlation between CRF and ADRs following chemotherapy. Barns and Bruera (13) reported that chemotherapy may be a primary cause of the fatigue experienced by cancer patients. Several other studies demonstrated that there is a significant correlation between fatigue and clinical characteristics. In a cohort study including 212 breast cancer patients, Goldstein *et al* (14) reported that fatigue in cancer patients was associated with clinical stage, age, treatment modality, menstrual status and the serum level of certain biochemical factors. Curt *et al* (15) reported data collected via telephone interviews from 379 cancer patients who had been treated with chemotherapy, which indicated that 90% of the patients experienced fatigue associated with the ADRs to chemotherapy, including gastrointestinal reactions, alopecia, weight loss and menopause. According to the previous studies, it was also confirmed that ADRs may cause fatigue. However, the number of studies investigating the correlation between CRF and ADRs to chemotherapy in lung cancer patients is currently limited.

In this cohort study of 100 lung cancer patients, we demonstrated that 88% of the patients experienced CRF. This finding was consistent with those of a previous study, indicating that the occurrence of CRF was 70-100% in lung cancer patients who had been treated with chemotherapy (16). CRF remains a major factor affecting patient QOL. Therefore, it is crucial to implement a preventive measure for symptom control of the ADRs to chemotherapy (17). In this study, we confirmed that the increased plasma levels of TNF-α and IL-1 exhibited a statistically significant correlation with CRF. It may be helpful to determine the CRF of a patient by measuring the plasma levels of TNF-α and IL-1 prior to and following chemotherapy, in order to guide the implementation of personalized therapy and limit the occurence of ADRs, thus minimizing the patients' suffering.

We also demonstrated that the development of ADRs following chemotherapy was significantly correlated with urine 17-OHCS levels. This finding suggests that 17-OHCS may be used as an indicator for predicting the occurrence of ADRs to chemotherapy. Therefore, pharmacological or non-pharmacological interventions may be undertaken to reduce 17-OHCS levels, in order to avoid the occurrence of post-chemotherapy ADRs.

In summary, plasma TNF-α and IL-1 levels are significantly correlated with CRF in non-small-cell lung cancer patients. In addition, increased urine levels of 17-OHCS may predict ADRs to chemotherapy. By testing these biomarkers in the clinical practice, certain pharmacological or non-pharmacological interventions may be implemented to achieve personalized treatment and improve the QOL of the patients.

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References

1. Bennett B, Goldstein D, Lloyd A, *et al*: Fatigue and psychological distress - exploring the relationship in women treated for breast cancer. Eur J Cancer 40: 1689-1695, 2004.
2. Armstrong TS, Cohen MZ, Eriksen LR, *et al*: Symptom clusters in oncology patients and implications for symptom research in people with primary brain tumors. J Nurs Scholarsh 36: 197-206, 2004.
3. Barton-Burke M: Cancer-related fatigue and sleep disturbances. Further research on the prevalence of these two symptoms in long-term cancer survivors can inform education, policy and clinical practice. Am J Nurs 106 (Suppl 3): 72-77, 2006.
4. Dodd MJ, Miaskowski C and Lee KA: Occurrence of symptom clusters. J Natl Cancer Inst Monogr 2004: 76-78, 2004.
5. Morrow GR, Shelke AR, Roscoe JA, *et al*: Management of cancer-related fatigue. Cancer Invest 23: 229-239, 2005.
6. Saligan LN and Kim HS: A systematic review of the association between immunogenomic markers and cancer-related fatigue. Brain Behav Immun 26: 830-848, 2012.
7. Wang XS, Williams LA, Krishnan S, *et al*: Serum sTNF-R1, IL-6 and the development of fatigue in patients with gastrointestinal cancer undergoing chemoradiation therapy. Brain Behav Immun 26: 699-705, 2012.
8. Orre IJ, Murison R, Dahl AA, *et al*: Levels of circulating interleukin-1 receptor antagonist and C-reactive protein in long-term survivors of testicular cancer with chronic cancer-related fatigue. Brain Behav Immun 23: 868-874, 2009.

9. Zhang S, Zeng D, Peng Y, *et al*: Cancer-related fatigue and chemotherapy-associated adverse effects: correlation with TNF-α, IL-1 and 17-hydroxylcorticosteroids. Future Oncol 10: 1619-1626, 2014.
10. Goldstraw P: The 7th edition of TNM in lung cancer: what now? J Thorac Oncol 4: 671-673, 2009.
11. Beasley MB, Brambilla E and Travis WD: The 2004 World Health Organization classification of lung tumors. Semin Roentgenol 40: 90-97, 2005.
12. Okuyama T, Akechi T, Kugaya A, *et al*: Development and validation of the cancer fatigue scale: a brief, three-dimensional, self-rating scale for assessment of fatigue in cancer patients. J Pain Symptom Manage 19: 5-14, 2000.
13. Barns EA and Bruera E: Fatigue in patients with advanced cancer: a review. Int J Gynecol Cancer 12: 424-428, 2002.
14. Goldstein D, Bennett B, Friedlander M, Davenport T, Hickie I and Lloyd A: Fatigue states after cancer treatment occur both in association with and independent of, mood disorder: a longitudinal study. BMC Cancer 6: 240, 2006.
15. Curt GA, Breitbart W, Cella D, *et al*: Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. Oncologist 5: 353-360, 2000.
16. Wagner LI and Cella D: Fatigue and cancer: causes, prevalence and treatment approaches. Br J Cancer 91: 822-828, 2004.
17. Yeh ET, Lau SC, Su WJ, *et al*: An examination of cancer-related fatigue through proposed diagnostic criteria in a sample of cancer patients in Taiwan. BMC Cancer 11: 387, 2011.