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Risk factors for serious adverse events due to cytotoxic chemotherapy for advanced non-small cell lung cancer

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ABSTRACT

Background: Chemotherapy is a standard treatment for patients with advanced non-small cell lung cancer (NSCLC); however, it occasionally causes adverse events. Serious adverse events (SAEs) are defined as any untoward medical occurrence that is related to drug use and results in life-threatening experiences, prolonged or initial hospitalization, or significant or persistent disability. However, as few studies have reported on the risk factors for SAEs, we aimed to identify the factors that could predict SAEs in NSCLC.

Patients and methods: We retrospectively reviewed the medical records of patients treated with pemetrexed plus cisplatin (PC), paclitaxel plus carboplatin plus bevacizumab (BVCP), docetaxel monotherapy (DTX), or pemetrexed monotherapy (PEM) at Juntendo University Hospital between January 2010 and March 2012. Two investigators reviewed the clinical records and judged SAEs. Multivariate analyses were performed to identify independent risk factors for SAEs among the following factors: gender, age, performance status, line of chemotherapy, preexisting interstitial lung disease (ILD), smoking status, and chemotherapeutic regimen.

Results: A total of 252 patients received chemotherapy (male/female, 162/90; median age [range], 66 years [36–92 years]; stage III/stage IV/postoperative recurrence, 53/145/54; adenocarcinoma/squamous cell carcinoma/not otherwise specified, 211/24/17; PC/BVCP/PEM/DTX, 50/ 51/ 67/ 84). Of these, 30 (11.9%) patients experienced SAEs. The SAEs were anorexia/nausea in 10 patients, febrile neutropenia (FN) in eight, drug-induced ILD in six, infection (sepsis, pleural infection, soft tissue infection) in three, elevated creatinine level in one, pneumothorax in one, and gastric hemorrhage in one. Treatment-related death was noted in four patients, two with drug-induced ILD, one with FN, and one with infection. Multivariate analysis revealed that preexisting ILD (odds ratio=5.06; p=0.0012) and the chemotherapeutic regimen (p=0.00-0.03) were significantly associated with SAEs.

Conclusions: Preexisting ILD and the chemotherapeutic regimen were risk factors for the prediction of SAEs in the treatment of NSCLC in clinical practice.

1. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases, and in more than half of these cases, patients present with advanced-stage disease at the initial diagnosis [2]. Systemic chemotherapy is the standard treatment for patients with advanced NSCLC without known driver mutations such as epidermal growth factor receptor mutation or anaplastic lymphoma kinase translocation. Currently, cisplatin plus pemetrexed (PC) or carboplatin plus paclitaxel plus bevacizumab (BVCP) is the standard front-line chemotherapy regimen, and docetaxel (DTX) or pemetrexed (PEM) is the standard second-line chemotherapy regimen for NSCLC patients[3–5].

Chemotherapy improves the survival and quality of life of patients with advanced NSCLC; however, it occasionally causes serious adverse events (SAEs). SAEs are defined as any untoward medical occurrence that is related to drug use and results in life-threatening experiences, prolonged or initial hospitalization, or significant or persistent disability or requires intervention to prevent these outcomes [6,7]. In clinical trials, SAEs and treatment-related deaths (TRDs) have to be

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reported. However, SAEs are not usually reported or accurately described in clinical practice [8]. Furthermore, a high cost of healthcare is incurred for treating SAEs and ambulatory encounters [9]. In addition to healthcare cost, SAEs affect quality of life. Therefore, a detailed evaluation of SAEs in clinical practice is important. However, to date, there are few reports describing the predictive factors for SAEs and their detailed characteristics in the daily care of patients with NSCLC.

In this study, we retrospectively analyzed NSCLC data, focusing on SAEs associated with the four most popular chemotherapeutic regimens. Our goal was to be able to identify patients who are at a high risk for SAEs and accordingly provide more careful observation for such patients in daily clinical practice.

2. Patients and methods

2.1. Patients

We retrospectively reviewed the medical records of the NSCLC patients who were treated at Juntendo University Hospital between January 2010 and March 2012. The study subjects were consecutive patients who met the following inclusion criteria: (1) histologically or cytologically confirmed advanced NSCLC and (2) treatment with PC, BVCP, DTX, or PEM. Patients whose adverse events could not be followed for at least 4 weeks were excluded. The number of the patients was calculated cumulatively.

2.2. Data collection

We retrospectively reviewed the medical records of the patients' baseline characteristics before chemotherapy, including sex, age, Eastern Cooperative Oncology Group performance status (ECOG-PS), clinical stage, smoking status, and line of therapy. The tumor characteristics noted included histological subtype and tumor-node-metastasis (TNM) stage, according to the seventh edition of the Union for International Cancer Control staging system [10]. TNM staging was based on computed tomography (CT), magnetic resonance imaging, fluorodeoxyglucose positron emission tomography, and bone scintigraphy findings [10].

Preexisting interstitial lung disease (ILD) was diagnosed when an interstitial shadow was detected in both lung fields on a chest CT scan before treatment. Interstitial shadows were defined as reticular shadow, ground glass opacity, honeycombing, and traction bronchiectasis. Three pulmonologists (KS, TS, and MK) independently reviewed all pretreatment CT scans and chest X-ray films. Lymphangitis carcinomatosa, pulmonary infection, or heart failure was carefully distinguished from the diagnosis with preexisting ILD. The study was conducted in accordance with the Declaration of Helsinki.

2.3. Chemotherapy

The PC regimen comprised 75 mg/m^2 cisplatin on day 1 plus 500 mg/m^2 pemetrexed on day 1. The BVCP regimen comprised area under the curve 6 carboplatin on day 1 plus 200 mg/m^2 paclitaxel on day 1 plus 15 mg/kg bevacizumab on day 1. The DTX regimen comprised 60 mg/m^2 docetaxel on day 1. The PEM regimen comprised 500 mg/m^2 of pemetrexed on day 1. Chemotherapy was repeated every 3 or 4 weeks for up to four to six cycles, unless disease progression or unacceptable toxicity was observed or the patient refused further treatment. After four to six cycles of PC or BVPC induction therapy, maintenance therapy with pemetrexed or bevacizumab was administered. Antiemetics were administered as required in accordance with the American Society of Clinical Oncology guidelines. Primary prophylactic granulocyte colony stimulating factor (G-CSF) and prophylactic antibiotics were not administered. For patients who had developed grade 4 neutropenia or grade 3 febrile neutropenia during previous cycles of chemotherapy, secondary prophylactic G-CSF administration was allowed. As common antiemetic pre-medication, patients received granisetron (1 mg) , dexamethasone (9.9 mg intravenously on day 1, 8 mg orally on days 2-4), and oral aprepitant (125 mg on day 1, 80 mg on days 2–3) during chemotherapy for PC; palonosetron (0.75 mg) and dexamethasone (9.9 mg intravenously on day 1, 8 mg orally on days 2-3) during chemotherapy for BVCP; and dexamethasone (6.6 mg intravenously) before chemotherapy for PEM and DTX.

2.4. Evaluation of toxicity and definition of SAEs

The Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE), were used to identify and classify adverse events. In this study, we defined SAEs as any untoward medical occurrence that was related to drug use and resulted in (1) life-threatening experiences, (2) prolonged or initial hospitalization, (3) significant or persistent disability or (4) required intervention to prevent these outcomes.

SAEs were evaluated from the start of each chemotherapeutic regimen to 4 weeks after the last administration of the specific chemotherapeutic regimen. TRD was defined as death due to adverse events occurring within 4 weeks after the last administration of the specific chemotherapeutic regimen without clear evidence of any other cause of death. Three physicians (KS, TS, and MK) independently reviewed medical charts, and judged SAE. If there were disagreements, they were resolved through discussions among the investigators.

2.5. Statistical analysis

We investigated the associations between SAEs and potential risk factors at the time of diagnosis. The following potential risk factors were investigated by both univariate and multivariate analyses: sex, chemotherapeutic regimen, age (≥75 years versus < 75 years), ECOG-PS (2-4 versus 0-1), creatinine increased before treatment (CTCAE grade 1 or more versus grade 0), hepatic dysfunction before treatment (CTCAE grade 1 or more versus grade 0), smoking status (≥30 pack-years versus < 30 pack-years), and preexisting ILD (presence versus absence). Hepatic dysfunction is evaluated based on following abnormal laboratory findings by CTCAE; blood total bilirubin increased, aspartate aminotransferase increased, alanine aminotransferase increased and alkaline phosphatase increased. The threshold of age "75" was selected because in the previous report, patients aged 75 or older had higher rates of adverse events during chemotherapy compared with patients younger than 55 years and this observation was independent of comorbidity [11]. The threshold of smoking status was selected because 30 pack year was the threshold at which patients are at high risk for lung cancer in U.S. Preventive Services Task Force. [12].

Binary and categorical variables were examined for association with SAEs by univariate analysis using the $\chi 2$ test or Fisher's exact test, as appropriate. Multivariate logistic regression analysis was performed to identify independent risk factors for SAEs. All tests for statistical significance were two-sided. All p-values less than 0.05 were considered statistically significant. All statistical analyses were performed using JMP, version 9.0 (SAS Institute Inc, Cary, NC, USA).

3. Results

3.1. Patient characteristics

Between January 2010 and March 2012, a total of 252 patients were enrolled in this study. Patient characteristics are shown in Table 1. Of these, 164 (65.1%) were male and the median age was 66 years (range, 36–92 years). The numbers of patients who received each regimen were as follows: PC, 50 (19.8%); BVCP, 51 (20.2%); DTX, 84 (33.3%); and PEM, 67 (26.6%). The histological subtype was adenocarcinoma in 211 (83.7%) patients, squamous cell carcinoma in 24 (9.5%) patients, and not otherwise specified in 17 (6.7%) patients. With