Lung Cancer 118 (2018) 41–47

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Prognostic significance of ^{18}F-fluorodeoxyglucose uptake of bone marrow measured on positron emission tomography in patients with small cell lung cancer

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ARTICLE INFO

Keywords:
^{18}F-fluorodeoxyglucose
Positron emission tomography
Small cell lung cancer
Bone marrow
Prognosis

ABSTRACT

Objectives: We investigated whether ^{18}F-fluorodeoxyglucse (FDG) uptake of bone marrow (BM) on positron emission tomography/computed tomography (PET/CT) has implications for predicting clinical outcomes in patients with small cell lung cancer (SCLC).

Methods: We retrospectively enrolled 70 SCLC patients who underwent FDG PET/CT prior to treatment. On PET/CT, maximum FDG uptake of all tumor lesions (Tmax), coefficient of variation (COV) of FDG uptake of primary tumor, and mean FDG uptake of BM (BM SUV) were measured. The relationships of BM SUV with PET/CT parameters of SCLC and serum markers were evaluated. Univariate and multivariate analyses were performed to assess the significance of BM SUV for predicting progression-free survival (PFS) and overall survival (OS).

Results: BM SUV had significant positive correlations with Tmax, COV of primary tumor, white blood cell count, and serum C-reactive protein level ($p < .05$). On univariate analysis, BM SUV showed significant association with only PFS ($p = .006$). On multivariate analysis, Veterans Administration Lung Cancer Study Group (VALSG) stage, N stage, M stage, Tmax, and BM SUV were independent prognostic factors for PFS ($p < .05$) and, for OS, VALSG stage and M stage were independent prognostic factors ($p < .05$). Among patients with limited disease, patients with high FDG uptake of BM had significantly worse PFS than did those with low FDG uptake of BM ($p < .05$), but, there was no significant difference in PFS between patients with extensive disease and patients with limited disease and high FDG uptake of BM ($p > .05$).

Conclusion: FDG uptake of BM was an independent predictor of disease progression in SCLC patients. Patients with limited disease and high FDG uptake of BM had similar PFS to those with extensive disease.

1. Introduction

Small cell lung cancer (SCLC) accounts for 10–15% of all cases of lung cancer and is notable for its aggressiveness and dismal prognosis, showing a 5-year survival rate of less than 5% [1,2]. The Veterans Administration Lung Cancer Study Group (VALSG) staging system has been generally used for staging SCLC, categorizing into two stages: limited disease (LD) and extensive disease (ED) [3]. However, because the American Joint Committee on Cancer (AJCC) TNM staging system has been shown to better differentiate survival than the VALSG staging system in patients with SCLC, the International Association for the Study of Lung Cancer recommended using the AJCC TNM staging as the standard [3,4]. Typically, LD SCLC is treated with a combination of chemotherapy and thoracic radiotherapy, and ED SCLC is treated with chemotherapy, but, for patients with TNM stage I SCLC, surgical resection has shown beneficial effects on survival [3,5]. In addition to tumor stage, previous studies have shown that age, performance status, serum lactate dehydrogenase (LDH) and alkaline phosphatase levels, white blood cell count, and platelet count were significant prognostic factors for SCLC [6].

Recently, a number of studies have demonstrated that development, progression, and epithelial-mesenchymal transition of tumor cells are closely associated with inflammatory tumor microenvironment and host immune response [7,8]. Serum C-reactive protein (CRP) and

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https://doi.org/10.1016/j.lungcan.2018.01.020
Received 2 November 2017; Received in revised form 23 January 2018; Accepted 28 January 2018

neutrophil-to-lymphocyte ratio (NLR), calculated by dividing the neutrophil counts by the lymphocyte counts in the blood, are well-known serum inflammatory markers that can reflect systemic inflammatory response to various pathologic conditions including malignant diseases [9]. In patients with SCLC, the levels of serum CRP and NLR were significantly associated with the clinical outcomes, showing poor prognosis in patients with high serum CRP and NLR [10–12].

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) has been widely used in lung cancer and has shown its clinical usefulness in staging, evaluating treatment response, and predicting prognosis in patients with SCLC [13–15]. Many studies have revealed that FDG uptake of bone marrow (BM) can be increased in patients with acute inflammatory and malignant diseases and that it is related to serum inflammatory markers such as CRP, white blood cells and NLR, suggesting that increased FDG uptake of BM indicates BM activation due to systemic inflammatory response [16–18]. Considering the significant influence of host inflammatory response to cancer progression, FDG uptake of BM could have association with clinical outcomes in malignant diseases. Still, the prognostic significance of FDG uptake of BM for predicting survival has not been evaluated in patients with SCLC. Hence, in the present study, we aimed to investigate the prognostic value of FDG uptake of BM for predicting progression-free survival (PFS) and overall survival (OS) in patients with SCLC.

2. Materials and methods

2.1. Subjects

The institutional review board of our university approved this retrospective study, and the requirement to obtain informed consent was waived. The study has been carried out in accordance with the principles of the Declaration of Helsinki. Medical records of all patients who were diagnosed with SCLC in our medical center between January 2011 and June 2016 were retrospectively reviewed. Of these, a total of 70 patients who had undergone pre-treatment FDG PET/CT and any subsequent type of treatment were included in the study. We excluded patients who had received only supportive care without any palliative treatments, had coexisting acute inflammatory disease, or had coexisting or a history of another malignancy or bone marrow disease such as myelodysplastic syndrome. Prior to initiation of treatment, staging work-up examinations including blood tests, contrast-enhanced chest CT, bone scintigraphy, brain magnetic resonance imaging (MRI), and FDG PET/CT were performed in all patients. The interval between blood tests and PET/CT scan were within two days in all patients. Patients who were suspected of bone metastases on bone scintigraphy and/or FDG PET/CT underwent additional bone MRI for the diagnosis. Based on the results of the examinations, patients were stage based on the 7th Edition of the AJCC TNM staging system guidelines and the VALSG staging system. We classified patients with tumor involvement confined to one hemithorax and ipsilateral supraclavicular lymph nodes as LD. The patients with tumor involvement beyond the ipsilateral hemithorax, including malignant effusion and hematogenous metastasis were classified as ED. After staging work-up, the patients underwent surgical resection, concurrent chemoradiotherapy, or systemic chemotherapy according to their disease stage and clinical condition. Patients who had no evidence of brain metastasis on staging work-up and showed complete or partial response to the initial treatment underwent prophylactic cranial irradiation. For patients who underwent chemotherapy, response evaluation with imaging examinations was performed after every two cycles of chemotherapy. After the initial treatment, all patients were followed at regular intervals of every 3–6 months.

2.2. FDG PET/CT imaging

Patients were instructed to fast for at least six hours before PET/CT examination. After the confirmation of peripheral blood glucose level of < 150 mg/dL, FDG at a dose of 4.07 MBq/kg was intravenously given 60 min before the PET/CT scans, which were performed with a combined Biograph mCT 128 PET/CT scanner (Siemens Healthcare, Knoxville, TN, USA) from the skull base to the proximal thigh. CT scan was performed with 100 mA and 120 kVp without contrast enhancement. Immediately following the CT scan, PET scan was performed in 3D mode with a 1.5 min per one bed position. The CT data were used for attenuation correction, and the PET images were reconstructed using an iterative algorithm using TrueX and time-of-flight reconstruction (2 iterations and 21 subsets).

2.3. Image analysis

All PET/CT images were retrospectively assessed without knowing the patients' clinical outcomes. First, a volume of interest (VOI) was manually drawn on the primary tumor lesion and included the entire lesion in the axial, coronal, and sagittal planes. The maximum (Pmax), mean, and standard deviation of the standardized uptake value (SUV) of the primary lung cancer lesion were measured. The coefficient of variation (COV), which is defined as the standard deviation divided by the mean value of SUV in the tumor volume, was calculated for each primary tumor lesion. Afterward, spheroid-shaped VOIs were drawn for all the metastatic SCLC lesions to measure maximum SUV of metastatic lesions of SCLC. The maximum SUV among the tumor lesions including the primary lung cancer and metastatic lesions (Tmax) was recorded for each patient. Lastly, to measure FDG uptake of BM, a spheroid-shaped VOI was drawn over the vertebral body of at least six vertebrae from the thoracic and lumbar spines. Vertebral body of the spines in which metastatic bone lesions, severe osteoarthritic change, compression fracture, or post-operative change due to previous spinal surgery were found on FDG PET/CT or MRI was excluded from the measurement of FDG uptake of BM. According to the method used in previous studies [17,19], the mean SUV of each vertebral body was measured using an automatic isocontour set at 75% of the maximum SUV within each VOI. Mean SUV of the six selected vertebrae was defined as mean SUV of BM (BM SUV).

2.4. Statistical analysis

To investigate the relationship of BM SUV with FDG PET/CT parameters of SCLC, hematologic parameters, and serum markers, Spearman's correlation coefficients were calculated. The associations of the variables with PFS and OS were assessed using a Cox proportional hazards regression model for univariate and multivariate analyses. Survival time for PFS and OS was defined as the time between the day of diagnosis and that of detection of disease progression and the time until death, respectively. The follow-up of patients without disease progression or death was censored at the day of the last follow-up visit at our medical center. The continuous variables in the survival analysis were classified into two groups according to the cut-off values determined by maximally selected chi-square method. In the multivariate analysis, variables that showed $p < .05$ in univariate analysis were included. Hazard ratios with Wald 95% confidence intervals were provided for the Cox regression models. PFS and OS curves were estimated using the Kaplan-Meier method and the log-rank test was performed to assess survival differences. To compare survival between multiple groups, Bonferroni correction was used to account for multiple testing. The statistical tests were performed using R 2.13.0 software (The R Foundation for Statistical Computing, Vienna, Austria) and MedCalc statistical software version 18 (MedCalc, Ostend, Belgium). A $p < .05$ was considered statistically significant.