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Interstitial lung abnormalities in treatment-naïve advanced non-small-cell lung cancer patients are associated with shorter survival

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ABSTRACT

Objective: Interstitial lung diseases are associated with increased risk of lung cancer. The prevalence of ILA at diagnosis of advanced non-small-cell lung cancer (NSCLC) and its impact on overall survival (OS) remain to be investigated.
Materials and method: The study included 120 treatment-naïve stage IV NSCLC patients (53 males, 67 females). ILA was scored on CT prior to any systemic therapy using a 4-point scale [0 = no evidence of ILA, 1 = equivocal for ILA, 2 = suspicious for ILA, 3 = ILA] by a sequential reading method previously reported. ILA scores of 2 or 3 indicated the presence of ILA.
Results: ILA was present in 17 patients (14%) with advanced NSCLC prior to any treatment (score3: $n = 2$, score2: $n = 15$). These 17 patients were significantly older (median age: 69 vs. 63, $p = 0.04$) and had a heavier smoking history (median: 40 vs. 15.5 pack-year, $p = 0.003$) than those with ILA score 0 or 1. Higher ILA scores were associated with shorter OS ($p = 0.001$). Median OS of the 17 patients with ILA was 7.2 months [95%CI: 2.9–9.4] compared to 14.8 months [95%CI: 11.1–18.4] in patients with ILA score 0 or 1 ($p = 0.002$). In a multivariate model, the presence of ILA remained significant for increased risk for death (HR = 2.09, $p = 0.028$) after adjusting for first-line systemic therapy (chemotherapy, $p < 0.001$; TKI, $p < 0.001$; each compared to no therapy) and pack years of smoking ($p = 0.40$).
Conclusion: Radiographic ILA was present in 14% of treatment-naïve advanced NSCLC patients. Higher ILA scores were associated with shorter OS, indicating that ILA could be a marker of shorter survival in advanced NSCLC.

1. Introduction

Lung cancer continues to be a leading cause of cancer death for both men and women in the United States [1]. Interstitial lung diseases, characterized by lung parenchymal damages due to various patterns of inflammation and fibrosis, were shown to be associated with the development of lung cancer, presumably because inflammation and fibrosis give rise to genetic damage which lead to lung parenchymal carcinogenesis and ultimately to cancer [2–6]. Interstitial lung diseases are also associated with smoking, which is one of the most clearly established risk factors and continued smoking is associated with shorter survival in patients with lung cancer [3,4,7–9]. Some prior reports have identified the similarities between the pathogenesis of interstitial lung diseases and smoking-related carcinogenesis, in the aspects of oxidative stress, mutagenesis, angiogenesis, and epithelial to mesenchymal transformation [2,10,11]. It is also well established that interstitial lung diseases may be exacerbated in lung cancer patients after local or systemic therapy which can adversely impact the clinical outcome [12–15]. However, the prevalence of interstitial lung diseases at the time of diagnosis and prior to initiation of treatment and the impact on survival among advanced lung cancer patients have not been systematically investigated.

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Computed tomography (CT) of the chest has been the primary modality to noninvasively assess the presence and severity of interstitial lung diseases. Washko et al. reported a sequential reading method for effective and efficient scoring of radiographic interstitial lung abnormalities (ILA) on chest CT using a 4-point scale [16,17], which has been applied to study the frequency of ILA in smokers from the COPDGene study, participants in the Framingham Heart Study, National Lung Screening Trial participants and other clinical cohorts of subjects at risk of lung cancer [17–22]. The application of the ILA scoring method to a cohort of patients with established diagnosis of advanced lung cancer may contribute to defining the frequency and severity of ILA in these patients and assess the impact of ILA on clinical outcome of patients with advanced lung cancer.

The purpose of the study is to determine the prevalence of interstitial lung abnormalities (ILA) detected on baseline chest CT in advanced NSCLC patients prior to the initiation of anti-cancer therapy, and investigate the association between ILA and survival duration while adjusting for smoking and other clinical characteristics. The study was carried out to determine if advanced NSCLC patients with smoking history have higher ILA scores than those without, and that patients with higher ILA scores have shorter overall survival compared to those with lower ILA scores.

2. Materials and methods

2.1. Patients

The study population included 120 patients with treatment-naïve stage IV (AJCC 7th edition) NSCLC who presented to the Dana-Farber Cancer Institute between August 2011 and July 2012, and had a baseline chest CT prior to the initiation of systemic therapy available for review. These 120 patients resulted from the selection of patients who satisfied these eligibility criteria. Clinical record of the demographics including age, gender, and race, clinical characteristics, and survival, as well as CT studies were retrospectively reviewed with the institutional review board approval. The patients in the study provided written informed consent. The specific items reviewed in the medical records included age, gender, and race, smoking history, pack years of smoking, histology, the presence or absence of distant metastasis (M1b or M1a disease), types of systemic therapy for lung cancer, and survival. Among the 120 patients, 83 patients received systemic chemotherapy, 28 received tyrosine kinase inhibitor therapy, and 9 patients received no systemic therapy.

2.2. CT scan of the chest

The standard clinical chest CT protocol at the DFCI utilized a 64-row MDCT scanner (Aquilion 64; Toshiba America Medical Systems, CA). Patients were scanned in the supine position from the cranial to caudal direction from the clavicles to the adrenal glands at end-inspiration. 100 mL of iopromide (Ultravist 300, 300 mg iodine/mL; Bayer HealthCare Pharmaceuticals Inc, Wayne, NJ) was injected intravenously with an automated injector (Medrad, Pittsburgh, PA) at a rate of 3 mL/s, with a scan delay of 30 s, unless medically contraindicated. The parameters were as follows: 0.5 mm collimation, 120 kVp, 0.5-s gantry rotation time and table speed of 53 mm per rotation. Tube current was determined by dose modulation with noise index of 15.0 Hounsfield Units (HU).

Axial images (5 mm thickness) are reconstructed using standard and lung algorithms. For the purpose of ILA scoring, axial images reconstructed with a lung algorithm were reviewed on Picture Archiving Communication Systems (PACS) workstations (Centricity, GE Healthcare) with a window level of −700 HU and a window width of 1500 HU as previously described [16].

2.3. Scoring of ILA using a sequential reading method

Retrospective imaging review was performed on baseline chest CT obtained at the time of diagnosis of NSCLC and prior to the initiation of systemic therapy. The baseline CT scan performed within ±12 weeks of the date of diagnosis of NSCLC (median time from the date of diagnosis to baseline CT: −0.6 weeks, range: −11.6 to +11.9 weeks) was selected for each patient. For 9 patients who did not receive systemic therapy, a CT scan performed within ±12 weeks of the date of diagnosis of NSCLC was selected for each patient. When a patient underwent chest CT scans prior to and after the date of diagnosis that are within ±12 weeks, the scan prior to the date of diagnosis was consistently selected for review.

Visual CT scoring of ILA was performed using a sequential reading method with a 4-point scale system that has been previously described [16,17]. CT scans were scored by 3 readers (board-certified radiologists with expertise in thoracic imaging; M.N., T.A., and H.H.) as "0", no evidence of ILA, "1", equivocal for ILA, "2", suspicious for ILA, and "3", ILA. *Equivocal* for ILA (score of 1) was defined as focal or unilateral ground glass attenuation, focal or unilateral reticulation, and patchy ground glass abnormality (less than 5% of the lung). *Suspicious* for ILA (score of 2) was defined as follows: nondependent ground glass abnormality affecting more than 5% of any lung zone, non-dependent reticular abnormality, diffuse centrilobular nodularity with ground glass abnormality, honeycombing, traction bronchiectasis, non-emphysematous cysts, architectural distortion. ILA (score of 3) was defined as bilateral fibrosis in multiple lobes associated with honeycombing and traction bronchiectasis in a sub-pleural distribution [16,17]. In this cohort of patients with advanced NSCLC, the readers were instructed to disregard findings due to lung cancer involvement such as intraparenchymal metastasis and lymphangitic spread of tumor, based on the radiologic interpretation, when assigning scores for ILA.

In the sequential reading method, Radiologist 1 reviewed and scored all the CT studies (Fig. 1). Next, Radiologist 2 independently reviewed all the studies scored as 1, 2, or 3 by Radiologist 1, as well as randomly selected 20% of the studies with score 0 by Radiologist 1, being blinded to the scores by Radiologist 1. The studies with concordant scores by two radiologists received the final score based on the two reads. The studies with discordant scores by two radiologists were independently reviewed by Radiologist 3, who was blinded to the scores by Radiologists 1 and 2, and were assigned the final score with majority opinion as described previously [16,17]. For each reader, the CT scans were presented in a different random order.

2.4. Statistical analysis

Associations between ILA scores and disease characteristics and demographics were assessed using Fisher's exact test for categorical variables and Kruskal test for continuous variables. The ILA

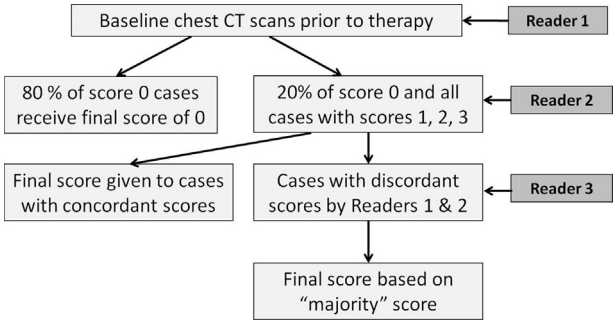

Fig. 1. Flowchart of the sequential reading method.