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Full Length Article

Incidence of Ct scan-detected pulmonary embolism in patients with oncogene-addicted, advanced lung adenocarcinoma

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ABSTRACT

Background: Patients with stage IIIB-IV lung adenocarcinoma are at high-risk for pulmonary embolism (PE). In these patients, EGFR and KRAS mutations as well as EML4/ALK rearrangements are recognized as "drivers" and as targets for therapy. Data on the incidence of PE in oncogene-addicted lung cancer patients are limited.
Aims: The aims of this study were to evaluate the incidence of CT scan-detected PE in patients with stage IIIB-IV lung adenocarcinoma and to assess the potential correlation between the presence of these oncogenes and the PE risk.
Methods: Baseline staging or re-staging chest contrast-enhanced CT scans of patients with stage IIIB-IV lung adenocarcinoma were retrospectively reviewed and adjudicated for the presence of PE. Data on the oncogene drivers (EGFR, KRAS or EML4/ALK) of the same patients were collected.
Results: A total of 173 patients with lung adenocarcinoma were included in the study. 24.8% of patients were EGFR mutated (31/125), 21.6% were KRAS mutated (27/125) and 13.6% hadan EML4/ALK rearrangement (17/125). 41 patients had a CT-detected PE (23.7%). A PE was observed in 5 patients with EGFR mutation (16.2%), in 5 patients with KRAS mutation (18.5%), in 8 patients with ELM4/ALK mutation (47.1%). The presence of ELM4/ALK rearrangement was associated with an increased risk of PE [HR:2.06 (95%CI 1.08- 3.55)]. Risk of PE was not found to be associated with EGFR or KRAS mutations.
Conclusions: Patients with advanced lung adenocarcinoma were at high risk for PE. The presence of EML4/ALK rearrangement was associated with an increased PE risk.

1. Introduction

The risk of venous thromboembolism (VTE) in patients with cancer is estimated to be about 4-fold greater in comparison with patients without cancer [1]. This risk varies across different cancer populations and it is generally higher in patients with advanced stages of disease [2,3]. In patients with lung cancer, the incidence of VTE is reported to be up to 14%, a 20-fold increased risk in comparison to the general population [4–6]. Non-small cell lung cancer (NSCLC) is associated with a VTE risk two-fold higher in comparison with small cell lung cancer (SCLC) [7]. Adenocarcinoma represents roughly 75% of NSCLC patients and is the most common subtype of lung cancer in the Western population. In the last decade, improved knowledge on biology of lung adenocarcinoma has led to the identification of specific oncogenic mutations such as EGFR and KRAS mutations [8,9]. EML4-ALK rearrangements have been more recently recognized as novel "drivers" for targeted agents in a subset of non-small cell lung cancers, mainly in patients with lung adenocarcinoma [10].These mutations, apart from rare exceptions, are mutually exclusive [8].According to the Lung Cancer Mutation Consortium data, one among the three mutations is detected in about 55% of patients with lung adenocarcinoma [11]. In Caucasian patients KRAS and EGFR are the most frequently detected mutations, with a rate of 25–30% and 10–15%, respectively. The frequency of EML4/ALK rearrangements is estimated to be around 3–7%.

A high rate of unexpected, CT scan-detected PE has been reported in patients affected by different types of malignancy, including lung cancer [12,13]. Patients with both symptomatic and unexpected CT scan-detected PE have a reduced survival compared to those without PE [14,15]. The aims of the study were to evaluate the incidence of CT scan-detected PE in patients with stage IIIB-IV lung adenocarcinoma harboring EGFR and KRAS mutations as well as EML4/ALK

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rearrangements and to assess the potential correlation between the presence of oncogene mutations and the rate of PE.

2. Materials and methods

Staging or re-staging chest contrast-enhanced CT scans and clinical records of consecutive patients, aged 18 years or older, with stage IIIB-IV lung adenocarcinoma, referred to Division of Medical Oncology at the Perugia Hospital between January 2010 and December 2012, were retrospectively reviewed. Patients were identified through the database of consecutive patients with lung cancer used at the Medical Oncology Service. Staging of patients with lung adenocarcinoma was performed according to the 7th lung cancer TNM classification and staging system [16]. In order to be included in the study, patients needed to undergo chest, contrast-enhanced, multi-detector row CT scan for cancer staging (both at baseline cancer staging and re-staging after chemotherapy regimens) or for confirming a clinical suspicion of PE. Both inpatients and outpatients were included. The exclusion criteria were: history of symptomatic VTE before baseline cancer diagnosis, the use of antithrombotic treatment for any indications and recent surgery (less than 3 months).

The follow up period was defined as the time between cancer diagnosis (at stage IIIB or IV) and death of patient, diagnosis of PE or the end of 2012.

Scans were performed on a 16-slice Multi-row Detector CT (MDCT) scanner, Lightspeed Ultra 16, General Electric, and on a 64-slice MDCT scanner, Aquilion 64, Toshiba. Each CT scanner was in use during the entire period of the study and the patients underwent both16 slices-CT scanner or 64 slices-CT scanner during baseline cancer staging or re-staging. All chest contrast-enhanced CT scans were adjudicated for the presence of PE. Formalin-fixed paraffin embedded (FFPE) tissues obtained at the time of diagnosis were analyzed simultaneously for EGFR (exon 18 to 21) and KRAS (exon 2 and 3) mutation status and for EML4/ALK rearrangement by fluorescence in situ hybridization (FISH) method. The following information of clinical records was collected at baseline cancer diagnosis: demographics characteristics, site, histological and staging of lung cancer, presence of oncogene mutations.

In case of pulmonary embolism, we also recorded the presence of a clinical suspicion of PE reported by attending physician on patients record before the positive CT-scan was performed.

Type of CT-scan employed to perform staging scans, type of chemotherapy, site of pulmonary embolism at pulmonary arteries, time between cancer diagnosis and PE diagnosis were also recorded.

Routine contrast-enhanced CT scans of the chest (one or more for each patients) were independently adjudicated for the presence of PE by three radiologists, unaware of the patients' clinical characteristics, type of cancer chemotherapy and the prior interpretation of the CT reports. Disagreements were resolved by consensus.

PE was defined as clinically unexpected if PE diagnosis was made on routine CT imaging in absence of a clinical suspicion of PE. In case of patients with clinical suspicion of PE, CT scans were anyhow reviewed to confirm the diagnosis.

The criteria for PE diagnosis were the presence of a filling defect in the pulmonary arteries that was classified as central, lobar, segmental, or sub-segmental, according to the location of emboli.

The correlation between PE and chemotherapy was analyzed in the subgroup of lung cancer patients in which a CT-detected PE was found at CT-scan restaging of cancer disease after chemotherapy. Patients with PE detected at the moment of cancer baseline or before starting chemotherapy were excluded from this analysis.

The smoking exposure of patients has been calculated in the packs/year, multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked [17]. Patients with lung adenocarcinoma were classified according to thesmoking history in never smokers, patients with smoking exposure of ≤20 packs/year, 20–100 packs/year and ≥100 packs/year or ex-smokers (if the smoking cessation was more than 10 years before).

Statistical analysis was performed with the Statistical Package for Social Sciences, Version 20 (SPSS) package (2013), using Chi Square Pearson's Test, and two-tailed binomial test. Hazard ratios (HR) for VTE and corresponding 95% confidence intervals (CI) were estimated using logistic regression models. Ethical Committee of the study center approved the study protocol.

3. Results

A total of 209patients with stage III-IV NSCLC were analyzed.Among these patients, 173 patients (87.2%) had adenocarcinoma, 30 (13.9%)squamous carcinoma, 2 large cell carcinoma, 2 BAC cancer and 2 NOS cancer. Among patients with lung adenocarcinoma, a total of 741 routine CT scan of the chest were reviewed; mean number of CT scan reviewed for patient was 4.3, with no differences between patients with and without a recognized oncogene driver. The mean follow up of patients with stage IIIB-IV lung adenocarcinoma was 507, 88 days (SD ± 243, 05). Not statistically significant differences in the mean follow up between patients with and without PE was observed: 460, 56 days (SD ± 214, 68); for patients without PE and 554,40 days (SD ± 191, 96) for patients with PE ($p = 0.216$).

A PE at chest CT scan was found 41 (23.7%) of these patients; in 3 of these patients (7.3%) a clinical suspicion of PE was made by the attending oncologist. Clinical Characteristics of the included patients with lung adenocarcinoma, according with the presence of CT-detected PE, are summarized in Table 1. Patients with PE had a median age of 58.5 ± 10.8 years and were males in 56.1%of the cases. Elevencases of PE were documented at the moment of cancer diagnosis or before starting of planned chemotherapy. A slight trend of CT-detected PE at baseline cancer diagnosis was observed in patients with stage III lung cancer in comparison with patients with stage IV lung cancer. Fourteen patients (34.2%) had a bilateral PE (Table 2). No statistical significant difference in terms of incidence of PE was observed between two different CT scanner.

125 of 173 patients with lung adenocarcinoma were analyzed for EGFR, KRAS mutation and ELM4/ALK rearrangement. At least one genetic alteration was found in 75 patients (60%). The EGFR mutation was found in 31 patients (24.8%), the KRAS mutation in 27 (21, 6%) and the EML4/ALK rearrangements in 17 (13.6%). No mutation was detected

Table 1
Demographic and clinical characteristics of patients with stage IIIB-IV, oncogene-addicted, lung adenocarcinoma according to the presence of PE.

	PE negative N = 132 (%)	PE positive* N = 41 (%)
Male gender	81 (61.3)	23 (56.1)
Mean age (SD)	64.3 (SD ± 9.5)	58.0 (SD ± 10.8)
Stage IIIB	11	7
Stage IV	121 (91.6%)	34 (83.1)
History of smoking		
Never smokers	38	18
Smoking exposure:	14	4
≤20 packs/year		
20–100 packs/year	43	12
≥100 packs/year	10	0
Ex-smokers	20	7
Unknown	7	0
At cancer diagnosis	na	11
Stable disease	na	15
Cancer in progression	na	12
Cancer in clinical remission	na	3
Cisplatin-based CHT (1° line)	56	17
Carboplatin-based CHT (1° line)	35	8
At least 1° CHT Line	128	22
More than 1 CHT line	54	19
Mean number of chest CT scans reviewed per patient	4.1	5.4

* 3 patients have a symptomatic, clinically suspected PE and 38 patients have a clinically unexpected PE.