Lung Cancer 121 (2018) 25–29

Contents lists available at ScienceDirect

Lung Cancer

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

# Impact of a comprehensive geriatric assessment to manage elderly patients with locally advanced non-small–cell lung cancers: An open phase II study using concurrent cisplatin–oral vinorelbine and radiotherapy (GFPC 08-06)

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ARTICLE INFO

*Keywords:*
Elderly patients
Locally advanced stage
Non-small-cell lung cancer
Radio-chemotherapy
Comprehensive geriatric assessment

ABSTRACT

*Introduction:* Few data have been published on the optimal management of elderly patients with locally advanced non-small–cell lung cancers (La-NSCLC). This prospective, multicenter, phase II study was undertaken to evaluate the ability of a comprehensive geriatric assessment (CGA) to select the elderly La-NSCLC patients who potentially may benefit from concurrent radio-chemotherapy.

*Methods:* The main inclusion criteria were: La-NSCLC, > 70 years old, at least one measurable target, ECOG performance status (PS) 0/1 and normal CGA. Weekly cisplatin (30 mg/m$^2$) and oral vinorelbine (30 mg/m$^2$) were combined with standard thoracic radiotherapy (66 Gy, 33 fractions) for 6.5 weeks. The primary evaluation criterion was < 15% clinically relevant grade > 2 toxicity. Secondary criteria were response rates, overall survival (OS) and progression-free survival (PFS).

*Results:* Among the 49 patients screened, 40 were included: 87.5% men, median age: 75.1 (70–84) years, 67.5% with PS 0, 52.5% squamous cell carcinomas. The full concurrent regimen was administrated in 77.5% of the cases (chemotherapy: 85%, radiotherapy: 90%); 22.5% of the patients experienced toxicity grade > 2 (with three treatment-imputed deaths), 15% when restricted to clinically relevant > 2 grade toxicities. One (2.6%) patient achieved a complete response, 53.8% had partial responses and 35.9% stable disease. Median PFS was 15 (95%CI: 8,7–35,2) months, OS 21.8 (95%CI: 16–NR) months and 1-, 2- and 4-year survival rates were 77.5%, 45% and 34.8%.

*Conclusion:* CGA was able to select fit elderly patients with La-NSCLCs eligible for concurrent chemoradiotherapy with a satisfactory risk/benefit ratio.

## 1. Introduction

Lung cancer is the leading cause of cancer mortality, with the median age of onset being 69 years for men and 67 years for women [1]. The recommended treatment of unresectable locally advanced non-small cell lung cancers (La-NSCLC) is concurrent chemoradiotherapy [2]. It is based on the results of several phase III trials and a meta-analysis based on individual patient data [3–8]. Compared to sequential

*Abbreviations:* ALK, anaplastic lymphoma kinase gene; CGA, comprehensive geriatric assessment; CT, computed-tomography scan; EGFR, epidermal growth-factor; ECOG PS, Eastern Cooperative Oncology Group performance status; La-NSCLC, locally advanced non-small–cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; CI, confidence interval; NR, not reached

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https://doi.org/10.1016/j.lungcan.2018.04.017
Received 20 February 2018; Received in revised form 15 April 2018; Accepted 19 April 2018

radio-chemotherapy, concurrent administration achieves better overall survival (OS), with a 4.5% benefit at 5 years, counterbalanced by 4%–18% more acute grade-3/4 oesophageal toxicity [4]. The most frequently used regimen combines poly-chemotherapy with a platinum salt and standard fractionated thoracic radiation (2-Gy fraction/day) delivering 66 Gy. In those trials, as for other NSCLC stages, elderly patients are under-represented [9]. Although age alone should not exclude fit patients, depriving them of standard treatment, concurrent chemoradiotherapy toxicity may limit its use in the elderly [10].

Few data are available on management of La- NSCLCs in elderly patients and most were secondary subgroup analyses [10–13]. In a phase II study on concurrent accelerated hyperfractionated radiotherapy and carboplatin–oral etoposide [14] that included 55 elderly patients with stage III NSCLCs, median OS was 10 months, and the 1-, 2-, and 5-year survival rates were 45%, 24%, and 9.1%, respectively, comparable to those obtained for younger patients. Toxicity appeared to be acceptable with hematologic, esophageal and bronchopulmonary acute grade-3/4 toxicities observed in 22%, 7% and 4% of the patients, respectively, and no grade-5 toxicity or late grade ≥3 toxicity. A secondary analysis of a phase III trial comparing chemotherapy plus bid or daily radiation for patients with stage III NSCLC [10] showed that the 2- and 5-year survival rates of patients > 70 years (26% of the randomized sample) did not differ from those of younger patients but the elderly had significantly more grade-4 toxicity, especially pneumonitis (1% of those younger < 70 years versus 6% of the elderly, $p = 0.02$). Those authors concluded that combined-modality therapy should be delivered with cautious and judicious monitoring of older patients.

Comprehensive geriatric assessment (CGA) may help select and monitor elderly patients' tolerance of therapy [15], as it can detect multiple health-related issues not reflected in the Eastern Cooperative Oncology Group performance status (ECOG PS) and comorbidity assessments, and its fitness determination appears to be associated with treatment completion. In a large randomized phase III study on elderly patients with advanced NSCLCs, CGA-based therapy allocation achieved less treatment-associated toxicity [16]. However, few data have been published on the impact of the CGA use for La-NSCLCs [17].

The objective of this study was to analyse the outcomes in terms of toxicity and survival of elderly patients selected by CGA parameters and treated by concurrent chemoradiotherapy.

## 2. Methods

### 2.1. Patients

Elderly patients with La-NSCLC selected with CGA and treated with concurrent chemoradiotherapy were included in this prospective, open, phase II study. The main inclusion criteria were: age > 70 years; histologically proven NSCLC; unresectable stage IIIAN2 or stage IIIB disease without pleural involvement or supraclavicular lymph-node invasion; at least one measurable target; PS score 0 or 1; < 10% weight loss; wild-type or unknown epidermal growth-factor–receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) gene status; normal hepatic, renal (creatinine clearance > 45 mL/min assessed with the Modification of Diet in Renal Disease equation) and hematologic parameters (hemoglobin > 9.5 g/dL), and satisfactory respiratory function ($FEV_1 \geq 40\%$ of theoretical value, $PaO_2 \geq 60$ mm Hg and KCO ≥ 60% of theoretical values). In addition, only patients deemed fit by CGA at screening by his or her regular oncologist were eligible. The domains explored, the scales used, and the definitions used to define a fit patient are described in Table 1. The protocol included no specific interventions to improve CGA-detected issues.

The main exclusion criteria were: active malignancy within the past 5 years, bronchoalveolar, neuroendocrine or composite cancer histology; superior vena cave syndrome and pleural effusion.

Pretreatment assessment included laboratory tests; chest X-ray; bronchoscopy; chest and brain computed-tomography (CT) scans; chest, brain and abdominal CT scans; bone scintigraphy; and pulmonary function tests. Mediastinoscopy was not mandatory. Positron-emission–tomography scan was not obtained systematically. Complete blood counts were done every week throughout the study. Patients underwent physical examinations at every chemotherapy cycle and every week during concurrent chemoradiotherapy.

**Table 1**
Domains Explored by the Comprehensive Geriatric Assessment and Fit-Patient Definition [16].

| Domain | Scales | Fit-Patient Definition |
|---|---|---|
| Functional status | ECOG-Performance Status | 0 or 1 |
| | ADL: Activities of Daily Living | 6 |
| | IADL: Instrumental Activities of Daily Living | 4 |
| Comorbidities | Charlson's index (no. of comorbidities) | 0 or 1: 70–79 years<br>0:79 years |
| Cognitive functioning | Folstein's Mini-Mental Status Examination | ≥24 |
| Geriatric syndrome | Fecal and/or urinary incontinence | None |
| Depression/mood | Geriatric Depression Scale 5 (GDS5), | 0 or 1 |
| Nutrition | Body mass index (BMI) | > 18.5 |
| Mobility | Timed Up and Go test | Properly done |
| Situational assessment | Accessibility of services, moving means, social environment, accessibility of the house rooms | Normal |

### 2.2. Treatment

Concurrent chemoradiotherapy consisted of thoracic radiotherapy, and weekly IV cisplatin (30 mg/m$^2$) and oral vinorelbine 30 mg/m$^2$ for 6 weeks. Radiotherapy (2 Gy/day, 5 days/week) was delivered to the primary tumor and involved lymph nodes for 6.5 weeks, for a total dose of 66 Gy in 33 fractions. Radiotherapy was delivered with photon beams generated by a linear accelerator with energy exceeding 6 MV, requiring personalized patient immobilization and conformational 3D-treatment planning, with a minimum of six radiation fields recommended. The planned target volume was the gross tumor volume plus a 1.5-cm margin without prophylactic nodal irradiation. The maximum dose delivered to any point in the spinal cord could not exceed 45 Gy. Dose-volume histograms were used to prevent pulmonary toxicity. V20 and V30 (total pulmonary volumes receiving 20 and 30 Gy, respectively) could be respectively ≤35% and 20% of total lung volume. If radiotherapy had to be interrupted for > 15 days because of toxicity, the patient was withdrawn from the study, but was included in the survival analysis. Each patient's radiation-therapy parameters (dose, radiation fields and dose–volume histograms) were centrally reviewed by a panel of radiotherapists. National Cancer Institute Common Toxicity Criteria version 3.0 were applied to evaluate toxicity. Therapeutic responses were assessed by CT scans 4 weeks after completing treatment. After the protocol treatment, chest X-rays were obtained every 3 months and thoracic CT scans every 6 months for 3 years. An independent panel reviewed the imaging studies for staging, toxicities and responses. After progression, investigator was free to choose the subsequent treatments.

### 2.3. Statistical analyses

The primary endpoint was the number of patients with grade > 2 clinically relevant adverse events (other than nausea and vomiting) and grade > 3 for hematological toxicity and asthenia. In published concurrent chemo-radiotherapy studies, grade-3/4 toxicity, others than grade 3 hemato-toxicity reached a maximum of 30%. A 50% reduction of that toxicity rate was considered clinically relevant. Secondary endpoints were objective response rate (ORR), OS and progression-free