Lung Cancer 81 (2013) 84–90

Contents lists available at SciVerse ScienceDirect

Lung Cancer

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

Randomized phase II trial of non-platinum induction or consolidation chemotherapy plus concomitant chemoradiation in stage III NSCLC patients: Mature results of the Spanish Lung Cancer Group 0008 study☆

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ARTICLE INFO

Article history:
Received 28 November 2012
Received in revised form 11 February 2013
Accepted 8 March 2013

Keywords:
Stage III non-small-cell lung cancer
Phase II randomized trial
Chemotherapy
Radiotherapy
Concurrent chemoradiation
Consolidation chemotherapy
Induction chemotherapy

ABSTRACT

The optimal schedule and regimen of chemotherapy (CT) in association with chemoradiation has not been established in stage III non-small-cell lung cancer (NSCLC). We have compared three schedules of non-platinum-based CT plus either radiotherapy or chemoradiation. From May 2001 to June 2006, 158 patients with unresectable stage III NSCLC were enrolled in a randomized phase II trial with overall response rate (ORR) as the primary endpoint. The initial design included three arms: sequential CT followed by thoracic radiation (TRT); concurrent CT/TRT followed by consolidation CT; and induction CT followed by concurrent CT/TRT. However, based on the preliminary results of the RTOG 9410 trial, the sequential arm was closed when 19 patients had been enrolled. All patients received two cycles of docetaxel 40 mg/m^2 days 1 and 8 plus gemcitabine 1200 mg/m^2 days 1 and 8, as either induction or consolidation therapy. Concurrent CT/TRT consisted of docetaxel 20 mg/m^2 and carboplatin AUC 2 weekly plus 60 Gy TRT. No differences were found in ORR between the two arms (56% and 57%). Hematological toxicity was mild but significantly superior with consolidation CT; the esophagitis rate was similar in both arms (16% and 15%). With a median follow-up of 57 months, no differences were found in median survival (13.07 and 13.8 months) or 5-year survival (16.4% and 22%). This regimen cannot be recommended as an alternative to platinum-based CT/TRT although it has an acceptable toxicity profile and encouraging long-term survival data (ClinicalTrials.gov NCT01652820).

1. Introduction

Lung cancer remains the leading cause of cancer-related death worldwide. Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all cases, and about one fourth of these have locally advanced disease [1], a complex and heterogeneous disease without a single, widely accepted standard of care. Unresectable, physically fit patients are usually treated with concurrent platinum-based chemotherapy (CT) and thoracic radiation (TRT) [2–4] but the optimal drugs, schedule, sequence and doses of CT when administered in combination with TRT have not yet been adequately defined [5].

☆ This study has previously been reported in part at the following meetings: 2005: American Society of Clinical Oncology Annual Meeting J Clin Oncol 23:16S, 2005 (abstr 7129); 2005: 11th World Conference on Lung Cancer Lung Cancer 49:S14, 2005; 2007: American Society of Clinical Oncology Annual Meeting J Clin Oncol 25:18S, 2007 (abstr 7620); 2007: 12th World Conference on Lung Cancer J Thorac Oncol 2:S365, 2007; 2008: American Society of Clinical Oncology Annual Meeting J Clin Oncol 26 suppl, 2008 (abstr 7574).

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0169-5002/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.lungcan.2013.03.009

Non-platinum-based regimens, in particular the combination of docetaxel and gemcitabine [6,7], have been proposed as a potentially less toxic alternative to platinum-based combinations for patients with advanced NSCLC. However, experience of this regimen in the stage III setting is limited, where the risk/benefit ratio needs to be even more finely balanced. The Spanish Lung Cancer Group (SLCG), therefore, conducted a phase II trial with a randomized selection design to examine the efficacy and toxicity of different sequences of docetaxel–gemcitabine in association with TRT in order to identify the most feasible regimen for further studies. Here we present the final results of this trial, including very mature survival data.

2. Patients and methods

2.1. Patients

All patients had histologic or cytological evidence of unresectable stage IIIA or IIIB (according to 6th TNM edition) NSCLC without pleural effusion or supraclavicular nodes. Only patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1 and weight loss $\leq$ 5% in the three months preceding the study were included. Other inclusion criteria were no prior systemic chemotherapy, granulocyte count $\geq$ 1500/mL, platelet count $\geq$ 100,000/mL, hemoglobin > 11 mg/dL, bilirubin < 1.5$\times$ normal, creatinine clearance $\geq$ 60 mL/min, preregistration forced expiratory volume in 1 s (FEV1) >30% or 1 L, measurable disease according to RECIST criteria, and a 3D planning computed tomography scan in the 21 days previous to the study entry that excluded a TRT planning treatment volume (PTV) $\geq$2000 cm^3 and/or a V20 $\geq$35%. Patients with active concurrent malignancy, serious medical or psychiatric illness, or history of serious cardiac disease were excluded. Diffusion lung capacity of carbon monoxide (DLCO) <30% was also an exclusion criteria. Women of childbearing potential had to have a negative urine or serum pregnancy test within the 7 days before study entry. The protocol (ClinicalTrials.gov identifier: NCT01652820) was reviewed and approved by the institutional review board at all participating institutions. All patients provided their signed informed consent before enrollment.

The pre-study evaluation included a complete medical history and physical evaluation, laboratory analysis, pulmonary function test (including DLCO), ECG, computed tomography scans of the chest and abdomen four weeks before study entry and a planning computed tomography scan. Computed tomography scans were used consistently for all evaluations and tumor measurements during the entire study period. A bone scan and brain magnetic resonance imaging were performed only if clinically indicated. Positron emission tomography (PET) was not available at the time the study was begun.

2.2. Study design

Initially all patients were randomly assigned to sequential CT and TRT (sequential arm), concurrent CT/TRT followed by consolidation CT (consolidation arm), or induction CT followed by concurrent CT/TRT (induction arm). However, based on the preliminary results of the RTOG 9410 trial [8], showing that concurrent CT/TRT was associated with longer survival compared to sequential CT and TRT ($p = 0.046$), the sequential arm was closed, and the study continued with only the two concurrent arms.

In both the consolidation and induction arms, all patients received two cycles of docetaxel 40 mg/m^2, days 1 and 8, plus gemcitabine 1200 mg/m^2, days 1 and 8. Concurrent treatment consisted of TRT plus docetaxel 20 mg/m^2 and carboplatin AUC 2 weekly. TRT consisted of 3D conformal irradiation of 2 Gy daily, five times per week, for a total dose of 60 Gy over six weeks. All patients received antiemetic therapy and standard dexamethasone in accordance with premedication recommendations for docetaxel.

Chest irradiation began on day 1 for the consolidation arm and on day 43 for the induction arm. The target volume consisted of an original (PTV1) and a boost (PTV2) volume. For both arms, the original volume was based on a planning CT scan taken before chemotherapy and included the primary lesion and any grossly involved nodal sites. Normal tissue tolerance criteria for the heart, spinal cord, and involved and uninvolved lung were mandated. Dose volume histograms were available. The target dose to the original volume was 44 Gy in 22 fractions of 2 Gy/fraction administered once daily Monday through Friday for 5 weeks without interruption by a linear accelerator generating photon beams superior to 4 MV, followed by a re-defined and re-planned target boost volume at 2.0-Gy fractions each day to a total dose of 60 Gy, using 1.0–1.5-cm normal tissue margins. The upper limit deviation allowed within the PTV1/2 daily TRT dose was 5%. Radiation was administered 1–2 h after completing chemotherapy (based on EORTC Radiotherapy Group guidelines).

2.3. Treatment modifications

Doses of drugs were reduced by 25% if febrile neutropenia or grade 4 thrombocytopenia lasted for more than five days. Chemotherapy was delayed for one week if the granulocyte count was less than 1.5×10^3/mL and/or the platelet count was less than 100×10^3/mL on the day of treatment. If granulocyte counts or platelet counts remained low for more than two weeks, chemotherapy was permanently discontinued.

During concurrent CT/TRT, the chemotherapy dose was reduced by 25% if the granulocyte count dropped to 1–1.49×10^3/ml and/or the platelet count dropped to 75–99×10^3/ml. If the granulocyte count fell below 1.0×10^3/mL or the platelet count below 75×10^3/mL, chemotherapy was omitted.

When a chemotherapy dose reduction was required, re-escalation of the chemotherapy dose was not allowed. Patients requiring more than one dose reduction were withdrawn from the study.

Interruption of radiotherapy was permitted for grade 3–4 esophagitis, grade 4 neutropenic fever or grade 4 thrombocytopenia. If radiation therapy interruptions of $\geq$10 days occurred, the patient was withdrawn from the study.

2.4. Assessment

Disease was assessed by computed tomography at the end of the first part of treatment and four weeks after the completion of all treatment. Follow-up studies included pulmonary function tests four weeks after the completion of all treatment. Subsequently, follow-up with computed tomography was performed every three months. For patients with complete response, a bronchoscopy was recommended at one year. Patients were removed from the protocol for disease progression, unacceptable toxicity, development of non-cancer-related illnesses precluding continued treatment, or patient request. Any treatment-related side effects were followed until resolution.

Tumor response was assessed according to RECIST criteria, but response to induction therapy did not require confirmation four weeks later. Toxicity was assessed using Common Toxicity Criteria (CTC) v2.0. An adverse event was reported as serious if it was fatal or life-threatening, required prolonged hospitalization, resulted in persistent or significant disability or incapacity, or was an important medical event. All patients receiving at least one dose of the study drug were evaluable for toxicity.