Lung Cancer 117 (2018) 32–37

Contents lists available at ScienceDirect

Lung Cancer

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

A phase III randomised study comparing concomitant radiochemotherapy with cisplatin and docetaxel as induction versus consolidation treatment in patients with locally advanced unresectable non-small cell lung cancer

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ARTICLE INFO

Keywords:
Lung cancer
Stage III
Radiochemotherapy
Randomised trial

ABSTRACT

Objectives: To assess if induction radiochemotherapy followed by consolidation chemotherapy (arm A) will improve survival in comparison with the same chemotherapy given as induction followed by consolidation concurrent radiochemotherapy (arm B) in patients with unresectable non-metastatic non-small cell lung cancer (NSCLC).

Patients and methods: Chemotherapy consisted in a combination of cisplatin with docetaxel, with one initial course for each patient, two courses in single modality therapy and weekly administration during chest irradiation (66 Gy).

Results: A total of 125 patients were randomised before early closure of the study because of poor accrual and an unplanned blind interim analysis which suggested that the continuation of the study would have been futile. Mature survival results showed no significant difference between both modalities with median survival times, respectively in arms A and B, of 19.6 months and 18.3 months, two years survival rates of 44% and 44% and five years survival rates of 23% and 26%. Toxicity was acceptable.

Conclusions: Our randomised study did not demonstrate survival difference between induction concurrent radiochemotherapy followed by consolidation chemotherapy and induction chemotherapy followed by consolidation concurrent radiochemotherapy.

1. Introduction

The addition of platinum-based chemotherapy to locoregional irradiation has significantly improved survival of patients with unresectable non-metastatic non-small cell lung cancer (NSCLC). Induction chemotherapy followed by radiotherapy has been shown better than radiotherapy alone [1]. Concomitant radiochemotherapy is associated with improved survival in comparison to the sequential administration of chemotherapy and radiotherapy [2].

In concomitant radiochemotherapy, the radiosensitisation properties of the platinum derivatives (cisplatin or carboplatin) are exploited. Other cytostatic agents can be used for that purpose such as gemcitabine (a pyrimidine analogous antimetabolite like cytarabine), the taxans paclitaxel and docetaxel (inhibitors of the depolymerisation of the tubulin molecules of the microtubules, leading to growth arrest in the G2/M phase of the cell cycle) and vinorelbine (a vinca-alcaloid inhibiting tubulin polymerisation). Gemcitabine and vinorelbine were used by our Group, the European Lung Cancer Working Party (ELCWP), in a prior randomised trial where both drugs were combined with cisplatin [3]. When our trial was designed, a recently published randomised phase III trial conducted in advanced and metastatic NSCLC [4] reported that cisplatin plus docetaxel was associated with better survival and reduced toxicity in comparison with cisplatin plus vinorelbine. At that time, a few studies showed that concurrent

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https://doi.org/10.1016/j.lungcan.2017.12.016
Received 18 July 2016; Received in revised form 22 December 2017; Accepted 27 December 2017

radiochemotherapy with cisplatin and docetaxel was feasible [5–9].

Radiochemotherapy can be administered with or without induction or consolidation chemotherapy. In 2006 when we designed the presently reported study, there was only one small published phase II randomised trial comparing late versus early radiochemotherapy [10]. The purpose of the phase III trial was to assess if induction concurrent radiochemotherapy followed by consolidation chemotherapy will improve survival in comparison with the same chemotherapy given as induction followed by consolidation concurrent radiochemotherapy, chemotherapy consisting in a combination of cisplatin with docetaxel.

2. Patients and methods

To be eligible, patients had to present with previously untreated initially unresectable (or inoperable for medical reasons) non metastatic stage III NSCLC (histologically or cytologically confirmed) without pericardial effusion or homolateral malignant pleural effusion and homolateral (except for upper lobe lesion) or heterolateral supraclavicular lymph node and had to have no functional or anatomical contra-indication to chest irradiation. An assessable or measurable lesion had to be present. Patients should not have prior history of malignancy except non melanoma skin cancer or in situ carcinoma of the cervix and "cured" malignant tumour (more than 5-year disease-free interval). Other eligibility criteria included Karnofsky performance status (PS) > 60, good renal (serum creatinine level < 1.5 mg/dl and/or creatinine clearance > 60 ml/min), hepatic (serum bilirubin level < 1.5 mg/dl, transaminases < 2.5× the normal value and phosphatase alkaline < 2.5× the normal value) and haematological (neutrophil count > 2000/ml and platelet count > 100,000/μl) functions. Patients presenting with recent (< 3 months before the date of treatment) myocardial infarction, active congestive heart failure or cardiac arrhythmia requiring medical treatment, uncontrolled infectious disease, symptomatic polyneuropathy, auditive impairment contra-indicating cisplatin administration or other serious medical or psychiatric illness precluding adherence to the study protocol were excluded. In addition, there should be no functional or anatomical contraindication to chest irradiation according to the protocol. Further, patients had to be accessible for follow-up and to have provided written informed consent.

Initial work-up included history and physical examination, complete blood sampling, electrocardiogram, pulmonary function tests, chest X-ray and CT scan, abdominal CT scan or ultrasound, cerebral CT scan or NMR, bone scan, bronchoscopy with biopsy. PET CT was not mandatory. Except for bulky involvement, mediastinoscopy was required in case of mediastinal nodes larger than 10 mm on CT scan and presumably metastatic or in case of positive PET scan. Blood counts were weekly performed. Blood chemistries, chest X-ray and clinical examination were repeated before each new course. Restaging with the same tests as during the initial work-up was performed 1 month after treatment completion. Patients were followed then every 2 months with clinical evaluation, chest X-ray and biological tests. Chest CT scan was checked every 6 months.

Eligible patients were randomised before any treatment at the ELCWP data centre to start the concomitant radiochemotherapy either with the 2nd cycle of chemotherapy (arm A) or with the 4th cycle of chemotherapy (arm B). Arm A consisted of an initial cycle of chemotherapy (CT) followed on day 22 by the concomitant radiochemotherapy and two additional cycle of CT and arm B of 3 cycles of CT followed on day 64 by the concomitant radiochemotherapy. The chemotherapy regimen (CD) was a combination of cisplatin and docetaxel. Docetaxel (75 mg/m^2) was given as a 60 min intravenous infusion, just followed by cisplatin (60 mg/m^2) that was administered over one hour, after pre-hydration with 1 l NaCl 0.9% over 3 h. One 1iter NaCl 0.9% in 3 h was administered as post-hydration. The recommended antiemetic regimen was a combination of dexamethasone and tropisetron. Courses were repeated every three weeks, as soon as haematological (neutrophils > 1500/mm^3 and platelets > 100,000/mm^3) and renal (creatinine < 1.5 mg/dl) functions had recovered. If myelosuppression persisted on day 36, the patient went off chemotherapy and was proposed for radiotherapy (if not yet received) without concurrent chemotherapy. If neutrophils nadir was < 500/mm^3 and/or platelets < 25,000/mm^3, doses of cytostatic agents were reduced to 75% for the next course, even if full recovery occurred at time of treatment.

During concurrent RT-CT, cisplatin (20 mg/m^2) and docetaxel (20 mg/m^2) were administered weekly for 6 courses. Both drugs were given each as a 30 min intravenous infusion, after pre-hydration with 1 l NaCl 0.9% over 1 h. One 1iter NaCl 0.9% in 1.5 h was administered as post-hydration. The recommended antiemetic regimen was a combination of dexamethasone and tropisetron. Chest irradiation had to start on the first day of concurrent RT-CT. Linear accelerator with an energy of 6 MeV or more was required and CT scan-based treatment planning was mandatory. Treatment planning should include anatomical regions with macroscopic malignant disease and safety margins for microscopic disease, patient's movement and beam or patient set-up uncertainties. The gross tumour volume (GTV) was defined as the primary tumour and lymph nodes larger than 1 cm in short axis dimension, plus any abnormal findings in bronchoscopy, mediastinoscopy, clinical examination or PET scan. The clinical target volume (CTV) encompassed regions at risk of microscopic extension. No elective mediastinal irradiation was performed. For the primary tumour, the margins were adapted to the displacements during breathing. Regarding the margins, 1 cm was added to the primary tumour and to involved nodes to take into account daily variations. The dose delivered to the CTV was 66 Gy with 2 Gy per fraction, 5 fractions per week. Lung inhomogeneity corrections were used. Variation within the target volume should not exceed 10%. Delivery of doses in excess of 45 Gy to the spinal cord and the whole heart was avoided. In case of positive mediastinal lymph nodes, adequate oblique fields were mandatory. Chemotherapy administration required neutrophils > 1000/mm^3 and platelets > 50,000/mm^3. If neutrophils were < 250/mm^3 and/or platelets < 10,000/m^3 during chemoradiotherapy, radiotherapy was delayed until the counts increased above 250/mm^3 or 10,000/mm^3, respectively.

During the whole treatment, the following rules for doses adaptation according to non-haematological toxicity were used. If the serum creatinine peak increased between 1.5 and 3.0 mg/dl with return to the normal value, the cisplatin dosage was reduced to 50%, except if creatinine clearance was > 60 ml/min. If serum creatinine peak exceeded 3.0 mg/dl, cisplatin administration was stopped. If serum creatinine peak was not in the normal range on day 28, the patient went off chemotherapy and proposed for radiotherapy alone, if not yet received. During RT-CT, if serum creatinine peak reached 1.5–3.0 mg/dl, cisplatin was omitted until recovery (creatinine < 1.5 mg/dl) and docetaxel was pursued; after recovery, the dose of cisplatin was reduced by 50%, except if creatinine clearance was > 60 ml/min. If serum creatinine peak has exceeded 3.0 mg/dl, cisplatin administration was stopped (even if return to normal value) and radiotherapy was continued with weekly docetaxel. In case of WHO grade > II neurotoxicity (peripheral polyneuropathy), chemotherapy was stopped. If hearing loss became evident, cisplatin administration was stopped.

Response was evaluated by a complete restaging after the end of the whole treatment. Response status, as well as the initial TNM stage [11], was assessed during regular meetings of the group by at least three independent observers. Complete remission was defined as the disappearance of all signs of disease. Partial response (PR), in measurable disease, was defined as a 50% or greater decrease of the total tumour load, without the appearance of new lesions or progression of any lesion. The tumour load was estimated as the tumour area calculated by the multiplication of the two longest diameters. In assessable disease, PR was defined as an estimated decrease in tumour size of 50% or more. Progression (PG) was considered to be an increase of greater than 25% in one or more measurable or assessable lesion or the appearance of a