Multicentre Phase II Trial of Paclitaxel and Carboplatin with Concurrent Radiotherapy in Locally Advanced Non-small Cell Lung Cancer

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Abstract. Aim: To evaluate weekly induction chemotherapy followed by weekly concomitant chemoradiotherapy in a multicentre phase II study of patients with unresectable stage III non-small cell lung cancer (NSCLC; stage wet IIIB excluded). Patients and Methods: Eligible patients received three weekly cycles of paclitaxel 100 mg/m² and carboplatin AUC2 followed by six weekly cycles of paclitaxel 60 mg/m² and carboplatin AUC2 in combination with thoracic radiotherapy (2 Gy per fraction and day to a total dose of 60 Gy). Results: Sixty-four patients (40 males and 24 females) with a median age of 63 years (range, 43-79 years) entered the study. T and N stage were distributed as follows: T1 2 patients (3.2%), T2 10 patients (15.6%), T3 15 patients (23.4%), T4 37 patients (57.8%); N0 10 patients (15.6%), N1 1 patient (1.6%), N2 26 patients (40.6%), N3 26 patients (40.6%), and N missing 1 patient (1.6%). Seven patients (10.9%) suffered from grade 3/4 oesophagitis. Grade 1/2 oesophagitis occurred in 36 patients (56.3%) and pneumonitis grade 1/2 occurred in 10 patients (15.6%). Sixty-three patients were evaluated on an intent-to-treat basis. The overall response rate was 74.6%. The median time to progression was 247 days and median overall survival was 461 days. According to subgroup analyses, no statistically significant differences were noted according to gender, age (<65 vs. ≥65 years), performance status, histology, or study centre. Conclusion: Induction chemotherapy followed by concurrent chemoradiotherapy with weekly cycles of paclitaxel and carboplatin is feasible and generates moderate toxicity. Efficacy is comparable to other recently published regimens. However, prognosis remains, in general, poor for this group of patients and further work to develop better therapy is required.

Annually about 3,000 new cases of lung cancer are diagnosed in Sweden (1). Non-small cell lung cancer (NSCLC) represents 75% to 80% of all lung cancer cases and one-third of these patients will have locally advanced disease not amenable to curative resection (2). Although advances have been made in the past two decades in treating this subset of patients, the progress has been slow. The 5-year survival rate is in the range of 5-13% (3).

The major controversies relate to the management of patients with stage IIIA disease. All three treatment modalities, surgical resection, chemotherapy and radiation, may be used in treating this stage. The ongoing debate focuses on which modalities to employ and in what sequence the treatment should be given. For patients with unresectable stage IIIA or IIIB disease, combined modality therapy (radiation therapy plus chemotherapy) is superior to radiation alone (4). However more recently, concurrent chemotherapy and radiotherapy appear to be superior to sequential therapy (5). Patient selection has an impact not
only on the response to therapy but also on how well the patient will tolerate it.

The reason for the poor prognosis is a high frequency of distant as well as local recurrences. Resection may be possible in some patients with NSCLC stage IIIA but is seldom curative due to the high frequency of micrometastases. Therefore treatment of stage III NSCLC should include combined modalities in order to increase survival. Chemotherapy improves survival when added sequentially to radiation therapy for patients with stage III NSCLC compared to radiation therapy alone (4, 6-9). Furthermore, median survival and 5-year survival rates are significantly longer and higher if chemotherapy is given concurrently (10, 11). Paclitaxel has substantial activity in stage IV NSCLC, either as a single agent (12-14) or in combination with carboplatin (15-19). The feasibility of giving these two agents simultaneously with radiotherapy to patients with locally advanced disease has also been studied (11, 20-22). Combined chemo- and radiotherapy for locally advanced NSCLC can now be considered as the standard treatment.

Paclitaxel acts as an antimitotic drug by inhibiting microtubuli depolymerisation and thus promoting stabilised tubuli which are unable to form the mitotic spindle (23). Another effect of paclitaxel is that of bcl-2 phosphorylation, promoting p53-independent apoptosis (24). Paclitaxel potentiates the effect of radiation by arresting the cells in the G2-phase, which is the most radiosensitive cell cycle phase. It may also increase apoptosis and tumour reoxygenation (25). Carboplatin can also effectively modulate radiation cell damage through such mechanisms as radiosensitisation of hypoxic cells, by inhibiting damage repair, by binding to thiols and by increased induction of chromosomal aberrations (6, 10, 26-28). Carboplatin may provide a higher platinum concentration in the cell at the time of irradiation compared to cisplatin (29).

Patient survival in stage III NSCLC is very poor and improved treatment strategies are needed, i.e. treatment where modalities of chemotherapy and radiotherapy are used in an optimal way. Weekly given paclitaxel results in a reduced toxicity relative to the every three week schedule and a more dose intense treatment is feasible (27). The primary objective in this multicentre phase II study was to evaluate the response rate in patients with inoperable stage III NSCLC receiving weekly paclitaxel and carboplatin together with radiotherapy. Secondary objectives were time to progression, survival and toxicity.

**Patients and Methods**

**Study centres.** Eight study centres participated in the study: Karolinska University Hospital in Stockholm, Lund University Hospital, Västerås Central Hospital, Southern Älvsborg Hospital in Borås, Linköping University Hospital, Gävle County Hospital, Karlstad Central Hospital and Norrland University Hospital in Umeå, Sweden.

**Eligibility criteria.** Patients with inoperable stage III NSCLC were eligible if they met the following criteria: Histologically or cytologically confirmed non-small cell bronchogenic carcinoma (squamous cell, adeno-, adenosquamous, undifferentiated, large cell, or bronchoalveolar carcinoma); unresectable or functionally inoperable patients; stage IIIA or stage IIIB according to TNM classification; age ≥18 years; at least one bidimensionally measurable lesion [measurable by chest X-ray or computed tomography (CT) scan]; not previously treated with chemotherapy or radiotherapy; performance status of 0-1 according to the WHO scale; life expectancy of more than 12 weeks; forced expiratory volume -1s (FEV₁) ≥1.0 l or ≥40% of expected volume; granulocyte count ≥1.5×10⁹/l; platelet count ≥100×10⁹/l; creatinine clearance measured by Cr-ErDA or Iohexol ≥40 ml/min; bilirubin ≤1.50x upper normal limit; patients written informed consent; all females of child bearing potential (WOCBP) were required to have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/l of β-HCG) within 72 hours prior to the start of study medication. All lab tests were performed no more than two weeks before therapy began.

Patients were excluded if having: NSCLC stage IIIB with malignant pleural effusion; past or current history of neoplasm other than that of the entry diagnosis, except for curatively treated basal cell cancer or carcinoma in situ of the cervix; significant history of cardiac disease, i.e. uncontrolled high blood pressure, unstable angina, congestive heart failure, myocardial infarction within three months, or cardiac ventricular arrhythmia requiring medication, history of 2nd or 3rd degree heart blocks; serious active infection at the time of inclusion or other serious underlying conditions which would impair the ability of the patient to receive protocol treatment; prior history of allergic reaction to drugs containing cremophor, e.g. cyclosporine-A, mannitol or vitamin-K; if pregnant or breast feeding, or not using adequate methods of birth-control; if having any other condition or therapy that, in the Investigator’s opinion, or as indicated in the product’s label could pose a risk to the patient or interfere with the study objectives; if having any other investigational drug given within 30 days of the initiation of study therapy, and participation in other clinical studies while enrolled in this protocol. Patients were not allowed to receive any other anti-neoplastic therapy (including biological response modifiers) while participating in this study.

**Treatment and follow-up.** Chemotherapy was given in an outpatient setting and consisted of paclitaxel (Taxol®) 100 mg/m²/week for three weeks, followed by a dose of 60 mg/m²/week for another 6 weeks given simultaneously with radiotherapy (given as a continuous infusion over 1 hour). Carboplatin (Paraplatin®) was given at a dose of AUC2, according to Calvert’s formula (carboplatin dose in mg = 2×[glomerular filtration rate (GFR)+25], per week for three weeks, followed by the same dose for another 6 weeks given simultaneously with radiotherapy (given as a continuous infusion over 15-30 minutes, 30 minutes after the paclitaxel infusion).

Radiotherapy started on week 4 of study treatment and was delivered as 2 Gy fractions (at reference point according to International Committee on Radiological Units Report 50) once daily Monday to Friday, to a total dose of 60 Gy without split courses. Radiation was interrupted in cases of leucopenia and thrombocytopenia grade 4 [white blood cell count (WBC) ≤1.0×10⁹/l, platelet count ≤25×10⁹/l] combined with fever and/or bleeding. The radiotherapy target volume consisted of the primary...
lung tumour plus a margin of 1.0-1.5 cm and gross lymph node metastases plus 2.0 cm margins in the crano-caudal direction and 1.0-1.5 cm in the lateral direction. The supraventricular fossa was not included in the target volume unless metastases were verified. Not more than half of the normal total lung volume was allowed to receive a dose above 20 Gy in 30 fractions. The maximum dose to the spinal cord was 45 Gy over 30 fractions.

Disease status by CT scan was reassessed after 3 weeks of concomitant treatment and 1 week after completing radiotherapy. Follow-up studies included CT scans every 3 months for the first 2 years and thereafter every 6 months. Patients were removed from the protocol for disease progression, unacceptable toxicity as assessed by the Investigator, development of intercurrent non cancer-related illnesses precluding continued treatment, patient non compliance with the protocol, or on the patient’s request.

**Study evaluation.** T and N substage were designated at the separate institutions. Toxicities were graded according to the NCI CTC, v2.0 (30). Tumour response was assessed according to the WHO. Patients were evaluable if they had received a minimum of 3 weeks of concomitant treatment with chemoradiotherapy and chemotherapy. A single-stage design according to the method of Fleming (31) required 56 response-evaluable patients to avoid: erroneously declaring the combination as sufficiently active for further investigations in spite of a true response rate <40% with a probability of 5% (type I error); erroneously rejecting the combination therapy as not sufficiently active (<40% ) in case of a true promising response rate ≥60% with a probability of 10% (type II error; power 90%). Taking into account the possibility of there being non-evaluable patients, a minimum of 60 patients were to be recruited. All analyses were carried out on an intent-to-treat basis (ITT). A two-sided 90% confidence interval for the response rate was calculated.

Time to progression was defined as the time from the first dose to time of progression or the end of the study. If a patient was classified with a progressive disease the date from such classification was used and if such, a date was missing, the date from the visit was recorded as progression date. Such a patient was recorded as an uncensored patient. If a patient was classified as having a response, the latest known date for such a patient was used in the calculations and the patient was recorded as a censored patient. For survival analysis, time to this endpoint was calculated as the time from date of first dose to either death or last follow-up. If a patient died, such a patient was classified as uncensored, otherwise as censored. Time to progression and the survival analysis were calculated using the Kaplan-Meier estimates along with graphs.

**Results**

**Patient characteristics.** Sixty-four patients with inoperable NSCLC stage III were included in the study. The median age was 63 years, with a range from 43 to 79 years. Forty patients were male and 20 were females. PS was 0 in 48 patients and 1 in 16 patients. Distribution of histology was as follows: squamous cell carcinoma in 20 patients (31.3%), large cell carcinoma in 6 patients (9.4%), adenocarcinoma in 25 patients (39.1%) and undifferentiated carcinoma in 13 (20.3%). The distribution of T and N status was as follows: T1 2 patients (3.1%), T2 10 patients (15.6%), T3 15 patients (23.4%), T4 37 patients (57.8%); N0 10 patients (15.6%), N1 1 patient (1.6%), N2 26 patients (40.6%), N3 26 patients (40.6%) and N missing 1 patient (1.6%).

**Treatment delivery.** Thirty-eight patients (59.4%) completed the prescribed nine weeks of treatment. Patients did not complete the whole prescribed treatment for the following reasons: progressive disease (2 patients), life-threatening toxicity (1 patient), lack of recovery of toxicity (3 patients), non-compliance with protocol (1 patient), Investigator’s decision (13 patients) and other reasons (6 patients). During chemoradiotherapy, 4 patients had their dose lowered and one had their dose delayed; paclitaxel was administered with a median dose of 180 mg and carboplatin was administered with a median dose of 250 mg. During concurrent chemoradiotherapy, 4 patients had their doses lowered and 22 patients had their dose delayed; paclitaxel was administered with a median dose of 107 mg and carboplatin was administered with a median dose of 250 mg. Radiotherapy doses were delivered well according to plan.

**Toxicity.** Maximum toxicities (chemotherapy and concurrent chemoradiotherapy) are shown in Table I. There was a low rate of grade 3/4 toxicities. Chemoradiation-associated oesophagitis grade 3 was observed in 6 patients (9.4%) and grade 4 in one patient (1.6%). There were no episodes of pneumonitis grade 3/4. However, 2 patients (3.1%) suffered from cough grade 3. Nausea/vomiting grade 3 occurred in one patient (1.6%) and fatigue grade 3 occurred in 4 patients (6.3%). There were no episodes of grade 3/4 neutropenia, thrombocytopenia, or infection. Oesophagitis, cough, nausea/vomiting and fatigue were the most frequent grade 1/2 toxicities.

**Response rate.** Sixty-three patients were available for evaluation. The best radiographic response was determined on an intent-to-treat basis. Of the 63 patients, 3 (4.8%) had a complete response, 44 (69.8%) displayed a partial response, 7 (11.1%) had stable disease and 7 (11.1%) had a

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<th>Toxicity</th>
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<td>Anaemia</td>
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<td>Neutropenia</td>
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<td>Oesophagitis</td>
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<td>Nausea/vomiting</td>
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<td>Peripheral neuropathy</td>
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<td>Alopecia</td>
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Table I. Haematological and nonhaematological toxicity.
progressive disease. Two patients (3.2%) had no or inadequate reassessment and were considered non-responders. The overall response rate was 74.6%. Univariate prognostic factor analyses for evaluable patients were performed. There were no significant differences according to gender, age (<65 vs. ≥65 years), performance status, histology, or study centre.

Time to progression and survival. Time to progression and overall survival was estimated according to the Kaplan Meier method for the 63 patients. The median progression-free survival based on radiographic criteria was 247 days (95% confidence interval, 187 to 373 days) and the 1-year progression-free survival rate was 40% (Figure 1). The median response duration for the intention-to-treat population was 241 days. Progressive disease was observed in 52 patients in total. The median overall survival was 461 days (95% confidence interval 347 days to not applicable, due to the fact that the last observation was censored) and the 1-year overall survival rate was 60% (Figure 2). Thirty-three patients died during the study and the follow-up. Univariate prognostic factor analyses for evaluable patients were performed both regarding time to progression as well as overall survival. No statistically significant differences were noted according to gender, age (<65 vs. ≥65 years), performance status, histology, or study centre.

Discussion

Prior to the recognition of the benefits of systemic chemotherapy for patients with metastatic NSCLC, the standard of care for patients with locally advanced unresectable or inoperable disease was radiation therapy. Initial clinical trials were not able to show improvements in prognosis in these patients when treated with non cisplatin-based chemotherapy in addition to thoracic radiotherapy (32, 33). On the contrary, in these studies the results were even worse in the chemoradiotherapy arms, with significant toxicity. However, subsequent randomized trials reported that cisplatin-based chemotherapy regimens in combination with thoracic radiotherapy improved both median survival as well as the proportion of long-term survivors (8, 9, 34-36). This difference may be due to the improved efficacy of the drugs used in the latter studies and also to their milder toxicity in combination with radiotherapy. The survival benefits in the combined modality arms may result from reduced metastasis rates as suggested by the data in the study by Le Chevalier et al. (8), as well as improved local disease control. A meta-analysis based on individual data demonstrated a statistically significant benefit of combining chemotherapy with radiation for these patients (4).

Long-term local disease control and control of distant metastasis remained unacceptably low in spite of combined chemoradiotherapy. More recent studies have compared alternative combined modalities. Median survival and overall survival rates were significantly longer in concurrently treated patients (median survival ranging from 16 to 24.5 months and the 1-year survival rate ranging from 54% to 68%) in several phase I/II studies evaluating the role of chemotherapy given sequentially or concurrently with thoracic radiotherapy (8, 20, 37-39). A recent individual patient-based meta-analysis examined the role of chemotherapy given either sequentially or concomitantly with radiation compared to radiation alone (40). Combined modality therapy improved survival (hazard ratio=0.88; p<0.001), corresponding to an absolute benefit in survival of 2.7% at 3 years. Concurrent chemotherapy also improved survival in a randomized trial comparing hyperfractionated radiotherapy versus hyperfractionated radiotherapy with
daily carboplatin/ etoposide (median survival of 14 months vs. 22 months and 4-year survival rates of 9% vs. 23%) (10). Concurrent therapy improves local tumour cytotoxicity and radiosensitivity even though these benefits are to some extent counteracted by enhanced toxicity in normal tissue, especially oesophageal toxicity (5).

However, prognosis for unresectable stage III NSCLC is very poor even if combined modality therapy is applied, irrespective of whether sequential or concurrent. We therefore set out in this multicentre phase II study to explore a novel protocol combining induction chemotherapy and concurrent chemoradiotherapy evaluating newer chemotherapy agents. Sixty-four patients with unresectable stage III NSCLC (stage wet IIIB excluded) received three weekly cycles of paclitaxel 100 mg/m² and carboplatin AUC2 followed by six weekly cycles of paclitaxel 60 mg/m² and carboplatin AUC2 in combination with thoracic radiotherapy (2-Gy fractions to a total dose of 60 Gy). Sixty-three patients were evaluable and analysed on an intent-to-treat basis. Our overall response rate was 74.6%, with a median time to progression of 247 days, median overall survival of 461 days, and a 1-year survival rate of 60%. According to subgroup analyses, no statistically significant differences were noted according to gender, age (<65 vs. ≥65 years), performance status, histology, or study centre. Our data confirm that a protocol combining induction chemotherapy and concurrent chemoradiotherapy is superior to chemotherapy and radiotherapy alone (41). Further more, these efficacy data are in line with other published phase II/III studies (42, 43).

Chemoradiotherapy generates significant toxicity and is sometimes limiting for treatment, or even lethal. Therefore it is of great importance to reduce both acute and long-term side-effects. In our study, 7 patients (10.9%) suffered from grade 3/4 oesophagitis. Other grade 3/4 toxicities were rare and no deaths occurred that were related to treatment. Grade 1/2 oesophagitis was most frequent, occurring in 36 patients (56.3%). Pneumonitis grade 1/2 occurred in 10 patients (15.6%) and no cases with grade 3/4 were recorded. Nausea/vomiting, fatigue and alopecia are well known side-effects and occurred relatively frequently (Table 1). Our protocol generated relatively mild to moderate toxicities and compares favourably with other chemotherapy regimens.

In several recent studies, paclitaxel and carboplatin were applied in combination with thoracic radiotherapy in unresectable stage III NSCLC. However, other new chemotherapy agents have also been explored. In a phase II study reported by Vokes et al., the patients were randomized to cisplatin/gemcitabine, cisplatin/paclitaxel, or cisplatin/ vinorelbine, concurrent with radiotherapy. Efficacy data were similar in all three groups (44). Consolidation therapy has also been examined with e.g. docetaxel in a phase III trial but without any improvement in overall survival (45). Thus, possibly a plateau has been reached with the presently available chemotherapy agents. Novel techniques for delivering radiotherapy could be one important way to improve therapy. Hyperfractionated accelerated radiotherapy (HART) and continuous hyperfractionated radiotherapy (CHART) have been shown to improve efficacy (10, 46). Further, radiotherapy delivered by stereotactic techniques may offer additional opportunities to improve local disease control (47). However, micrometastasis is, in the majority of cases, the limiting factor for long-term survival. Therefore combination therapies are absolutely required in patients with good performance status and no significant weight loss. These may be significantly improved by adding tumour- (and possibly tissue-) specific compounds such as antibodies and tyrosine-kinase inhibitors, which are of utmost interest and such studies are ongoing (48).

In conclusion, three weekly cycles of paclitaxel and carboplatin followed by six weekly cycles of paclitaxel and carboplatin combined with thoracic radiotherapy (2-Gy fractions to a total dose of 60 Gy) in patients with unresectable stage III NSCLC is feasible and generates relatively mild toxicity. Efficacy is comparable to that with other recently published regimens, and concurrent chemotherapy and radiation therapy produces the highest cure rates as measured by 5-year survival, but does so at an increased level of toxicity (49-51). However, prognosis is still in general poor for this group of patients and further work on protocols for chemotherapy and radiotherapy are required. Special emphasis should be made on to the addition of targeted and tailored compounds in this setting.

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References


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