Combination Chemotherapy with Paclitaxel and Gemcitabine Followed by Concurrent Chemoradiotherapy in Non-operable Localized Non-small Cell Lung Cancer. A Hellenic Cooperative Oncology Group (HeCOG) Phase II Study

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Abstract. *Concurrent chemoradiotherapy has become a standard therapy for locoregionally advanced inoperable non-small cell lung cancer (NSCLC). The purpose of this phase II trial was to evaluate the efficacy and toxicity of concurrent chemoradiotherapy following induction with non-platinum chemotherapy in patients with inoperable locally advanced NSCLC. Patients and Methods: All patients with locally advanced inoperable NSCLC ECOG performance status (PS): 0-1 following staging received paclitaxel 200 mg/m^2 in a 3-h infusion on day 1 and gemcitabine 1000 mg/m^2 on days 1 and 8 every 21 days for two cycles. The patients with a response or stable disease (SD) continued to receive paclitaxel 60 mg/m^2 weekly and radiotherapy 63 Gy given at 1.8 Gy once a day for 7 weeks. Results: Forty-three eligible patients entered the study. The median age was 63 years (range 42-76), male 93%, IIIB 63% and IIIA 37%. Following induction 15 (36.5%) of the patients responded: complete response (CR), 2%; partial response (PR), 33%; and 19 (46.5%) SD. From those with SD, 7 (37%) improved to a PR following concurrent chemoradiotherapy. With a median follow-up of 44 months (95% CI: range 36-53) the median survival was 20.8 months (95% CI: range 15.4-26.3) and time-to-progression 8.4 months (95% CI: range 6.2-10.6). The median survival of those who had improved response from SD to PR was 31.4 months (95% CI: range 18.7-44.1) versus 20.8 months (95% CI: range 5.5-11.3) for those who had no improvement ($p=0.20$). The commonest grade 3/4 toxicity in induction was neutropenia 12% with 2 febrile neutropenic patients whereas in the concurrent chemoradiotherapy neutropenia, neurotoxicity and oesophagitis were observed in 6% of the patients. Conclusion: Concurrent chemoradiotherapy following induction chemotherapy in patients with stage III NSCLC is feasible with reasonable efficacy and acceptable toxicity.*

Approximately 80% of all lung cancer cases are non-small cell lung cancer (NSCLC), and 25% to 40% of NSCLC patients have stage III, locally advanced disease (1, 2). Despite all new chemotherapy combinations the majority of these patients relapse and die of their disease within 2 years of diagnosis. In the last decade, radiotherapy has been the standard treatment for these patients. Several reports and meta-analyses (3, 4) have shown that combination chemoradiotherapy was superior to radiotherapy alone. Numerous clinical trials were conducted in the 1990s to determine the best combination of chemotherapy and radiotherapy and to examine whether concurrent chemoradiotherapy was appropriate in this setting (5-10).

The recent Cochrane meta-analysis which included three of the trials (6, 7, 9) found a significant reduction in risk of death at two years (RR 0.86 $p=0.003$) with concurrent therapy, but the toxicity results were not encouraging (11).

In the BROCAT German trial 2 cycles of induction chemotherapy were given and then randomisation (if no progression) to radiotherapy alone or radiotherapy with

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concurrent single agent paclitaxel. Median survival was 18.7 months on the chemoradiotherapy arm *vs.* 14.1 for the radiotherapy alone arm (10).

The CALGB 9431 Phase II trial randomised to two cycles of cisplatin and either gemcitabine, paclitaxel or vinorelbine induction followed by another 2 cycles of the same chemotherapy concurrently with radiotherapy (66Gy). Median survival was 17 months with no clear superiority between the regimens (12).

In the subsequent CALGB 9801 trial the patients were randomised to either immediate concurrent chemoradiotherapy (carboplatin AUC of 2 and paclitaxel 50 mg/m^2 each one given weekly during 66 Gy chest radiotherapy) or two cycles of induction chemotherapy with carboplatin AUC 6 and paclitaxel 200 mg/m^2 given q 21 days x 2 cycles followed by identical chemoradiotherapy. There was no significant survival difference between the two arms (13).

The SWOG 9504 trial used a standard concurrent platinum, etoposide - radiotherapy approach followed by three cycles of docetaxel. Despite the trial being non-randomised (14), the impressive median survival, of 26 months and 2 year survival of 54% has led to the regimen's general use.

Based on the above and our previous experience with the non-platinum combination paclitaxel/gemcitabine (15) we conducted a Phase II trial to evaluate the efficacy and toxicity of concurrent chemoradiotherapy with paclitaxel following induction chemotherapy with paclitaxel plus gemcitabine, in patients with inoperable locally advanced NSCLC, stages IIIA and IIIB. The primary end-point of this phase II study was to evaluate the response to chemoradiotherapy and then to evaluate toxicity, time-to-progression (TTP) and overall survival time.

Patients and Methods

Eligibility criteria. Patients with histologically or cytologically confirmed locally advanced stage IIIA or IIIB NSCLC, chemotherapy naïve, were eligible for the study. Criteria for entry into the trial also included PS (ECOG performance status) of 0 or 1, life expectancy of at least 12 weeks, males or females at least 18 years of age, adequate bone marrow reserve (white blood cell (WBC) count $\geq 4x10^9$/L, platelets $\geq 100x10^9$/L), and adequate renal (creatinine >60 ml/min), and liver function (bilirubin <1.2 mg/dl, γ-GT and ALP within normal range). The trial was approved by the ethical committees of the participating hospitals and all patients gave their informed consent to participate in the study.

Treatment. Following staging, all patients received induction chemotherapy, which consisted of two 21-day cycles of paclitaxel and gemcitabine. Paclitaxel was given at 200 mg/m^2 in a 3-h infusion on day 1. Gemcitabine was given at 1000 mg/m^2 *i.v.* over 30 min on days 1 and 8 of each 21-day cycle of induction chemotherapy (following paclitaxel on day 1). Antiemetics and other supportive care were provided at the treating physician's discretion. The use of growth factors was allowed for dose-limiting neutropenia or neutropenic fever at the treating physician's discretion.

During induction chemotherapy, dose reduction was necessary in patients with haematological toxicity. The next chemotherapy cycle started only if there was an absolute neutrophil count ≥1, 500/μL and a platelet count ≥100,000/μL and there was no non-haematological toxicity Grade 3 or 4, with the exception of alopecia.

Patients with an objective response or stable disease continued to receive paclitaxel 60 mg/m^2 weekly and radiotherapy 63 Gy given at 1.8 Gy once a day for 7 weeks.

Concurrent radiotherapy was planned to be delivered daily in 1.8 Gy single fractions 5 times a week to a total of 63 Gy over 7 weeks, commencing at least 3 weeks after the last dose of induction chemotherapy, provided there was complete resolution of chemotherapy-related toxicity, with the exception of alopecia. The 3-D conformal technique with a linear accelerator was used. The treatment was scheduled in two phases with the technique of shrinking fields.

Patients evaluation and statistical methods. Patient history, physical examination, evaluation of performance status, full blood count, biochemistry, chest X-ray and computed tomography (CT) scan of the thorax and upper abdomen, as well as bone scanning were obtained before treatment. Mediastinoscopy was not mandatory and was performed only at the treating physician's discretion. Positron emission tomography (PET) scan was not available.

The patients were assessed weekly for full blood count. Physical examination and biochemistry were also assessed at the initiation of each cycle. Tumour assessment was performed at baseline and every 3 weeks during treatment until progression. The objective tumour response was evaluated according to WHO criteria with the definition of stable disease (SD) requiring a duration of at least 4 weeks (16). Toxicities were graded according to the Revised Common Toxicity grading Criteria version 2 (17).

The primary end-point of the study was to evaluate the response of chemotherapy and radiotherapy. Therefore the study was designed to detect a response rate (partial, (PR) and complete response, (CR)) of 50% as compared with a minimal, clinically meaningful response rate of 30%. According to a two-stage design proposed by Simon, a sample of 19 patients would be required in the first step. If a minimum of seven responses was observed a total of 39 patients was required. If at least 17 responses occurred, the probability of accepting a treatment with a real response rate of less than 30% would be 5%. On the other hand the risk of rejecting a treatment, with a response rate of more than 50% would be 20%. Overall survival was defined from the date of the beginning of treatment to the date of death due to any cause. The analyses of survival were estimated by the Kaplan-Meier method and comparisons of survival were performed with the log-rank test.

Results

Patient's characteristics. The study was initiated on 13/12/2000 and the last patients entered the trial on 08/12/2003. The median follow-up was 44 months (range 3.3-62.0). Forty-three eligible patients with stage IIIA and IIIB entered the study. The median age was 63 years (range

42-76), males 93%, 63% had stage IIIB disease whereas 37% had stage IIIA. The predominant histology was squamous cell carcinoma (Table I).

Out of the 43 patients, 32 patients were eligible to continue with concurrent chemoradiotherapy. Eleven patients did not start chemoradiotherapy (one died after induction chemotherapy (IC), one discontinued IC after the 1st cycle due to grade 4 allergic reaction to paclitaxel, 7 patients progressed after the IC, one patient had a lobectomy and another had a pneumonectomy after the IC.

From the 32 eligible patients, 29 were evaluable (1 patient refused to be evaluated, one discontinued complete chemoradiotherapy due to toxicity and one patient died before evaluation, from the disease).

Compliance to treatment. Ninety-three cycles of induction chemotherapy were given. Eighty (86%) cycles were given at the full dose of gemcitabine and paclitaxel. Of the 32 patients who went on to have chemoradiotherapy 78% to 50 Gy or more of radiotherapy and 87% of the patients had 4 or more weekly cycles of paclitaxel. Twenty-two (69%) patients had CCRT (at least 4 weeks of paclitaxel and 50 or more Gy of radiotherapy).

During IC, 11 (26%) patients received GCSFand 8 (19%) patients received antibiotics. Out of the 32 patients that received chemoradiotherapy, 4 (12.5%) patients received GCSF and 8 (25%) antibiotics.

Response and survival. The response rate after induction gemcitabine and paclitaxel was 37% (95% confidence interval: range 21-50.9%), 35% PR and 2% CR, 46% of patients had stable disease (SD) and 7 patients (17%) progressed. After chemoradiotherapy, the overall objective response rate was 59% and the SD rate was 9.5%. One additional patient had a complete response following a partial response post IC. Seven additional patients (37%) showed a partial response after SD post IC.

Survival time. With a median follow-up of 44 months (95% CI: range 36-53) the median survival was 20.8 months (95% CI: range 15.4-26.3) and TTP 8.4 months (95% CI: range 5.5-11.3). The median survival of those whose response improved from SD to PR was 31.4 months (95% CI: range 18.7-44.1) *versus* 20.8 months (95%CI: range 4.4-37.3) for those who failed to improve ($p=0.20$).

Toxicity. The commonest grade 3/4 toxicity in IC was neutropenia 12%. However, only 2 out of the 43 patients experienced febrile neutropenia during 93 cycles of IC and IC was not associated with any grade 3 or 4 non-haematological toxicities except one patient who experienced a grade 4 allergic reaction to paclitaxel and 41% with alopecia. Also 9% grade 2 myalgias were observed and 7% of the patients experienced grade 2 pruritus. In the concurrent chemoradiotherapy, grade 3 neutropenia was observed in 6% of the patients, and 2 of them had febrile neutropenia. Non-haematological toxicity from chemo-radiotherapy included 6% grade 3 neurotoxicity and oesophagitis and 3% grade 3 allergic reactions. Most of the oesophagitis (56%) was grade 1/2. Pneumonitis grade 1/2 occurred in 22% of the patients (Table II) .

Table I. *Patient and tumour characteristics.*

No. of patients	43
Male/Female	40/3
Median age, years (range)	63 (42-76)
Clinical stage	
IIIa	16(37%)
IIIb	27(63%)
Eastern Cooperative Oncology Group status	
0	25(58%)
1	18(42%)
Primary site	
Left lung	13(30%)
Right lung	30(70%)
Histology	
Squamous cell carcinoma	22(51%)
Adenocarcinoma	16(37%)
Large cell carcinoma	1 (2%)
Non-small cell lung carcinoma, NOS	4(10%)

NOS: Non-otherwise specified.

Discussion

The treatment of stage III inoperable NSCLC remains controversial. Recent studies have shown that chemotherapy and radiotherapy are more efficacious when given concurrently at the expense of increased toxicity (5, 6, 8, 9). Although concurrent chemoradiotherapy has been accepted as standard treatment for fit patients with locally advanced stage III unresectable NSCLC, the possible benefit of induction chemotherapy over standard chemoradiotherapy is unproven.

In our study induction chemotherapy consisted of the new agents, gemcitabine and paclitaxel. This is a non-platinum combination of proven efficacy (15). The response rate of 35% is considered optimal. The overall median survival of 20.8 months is encouraging, compared to that reported in the literature (5, 6, 18, 19, 20). Vokes *et al.* have reported the results of induction chemotherapy followed by concurrent chemoradiotherapy where such new agents as gemcitabine, paclitaxel, or vinorelbine were used. That study showed favorable survival data with median overall survival of 17 months and a 1-year survival rate of 62-68% and 2-year survival rate of 29-40%, respectively. The median survival time for all patients was 17 months (13)

Table II. *Adverse events related to concurrent chemoradiotherapy.*

Drug related adverse event	No. of cycle (%) n=32	Maximum grade			
		Number and percentage of cycles by grade			
		1	2	3	4
Haematology adverse events					
Anaemia	12 (37.5%)	9 (28%)	3 (9.5%)	0 (0%)	0 (0%)
Leucopoenia	13 (41%)	7 (22%)	5 (16%)	1 (3%)	0 (0%)
Neutropenia	7 (22%)	4 (13%)	1 (3%)	2 (6%)	0 (0%)
Thrombocytopenia	1 (3%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Non-haematological adverse events					
Nausea	4 (13%)	4 (13%)	0 (0%)	0 (0%)	0 (0%)
Vomiting	5 (16%)	5 (16%)	0 (0%)	0 (0%)	0 (0%)
Alopecia	21 (66%)	4 (12.5%)	4 (12.5%)	13 (41%)	0 (0%)
Diarrhoea	2 (6%)	1 (3%)	1 (3%)	0 (0%)	0 (0%)
Neurotoxicity	10 (31%)	7 (22%)	1 (3%)	2 (6%)	0 (0%)
Myalgia/arthralgia	8 (25%)	8 (25%)	0 (0%)	0 (0%)	0 (0%)
Oesophagitis	20 (62.5%)	11(34.5%)	7 (22%)	2 (6%)	0 (0%)
Headache	1 (3%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
Infection	9 (28%)	2 (6%)	5 (16%)	2 (6%)	0 (0%)
Cough	2 (6%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)
Stomatitis	3 (9%)	2 (6%)	1 (3%)	0 (0%)	0 (0%)
Dermatitis	1 (3%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
Pneumonitis	7 (22%)	6 (19%)	1 (3%)	0 (0%)	0 (0%)
Allergic reaction	1 (3%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)

On the other hand, when docetaxel was used as consolidation chemotherapy following concurrent chemoradiotherapy in the SWOG 9504 trial the median survival was reported to be 26 months with 1- and 2-year survival rates of 76% and 54%, respectively (14).

It is important to emphasize that in our study, the median survival time for those patients who achieved a stable disease after induction chemotherapy and continued to receive chemoradiotherapy with paclitaxel, was 31.4 months for those whose response improved (37%) *versus* 20.8 months for those who did not respond and all of them tolerated the complete regimen. Certainly the number of patients is too small to make any definite conclusions but the trend is evident.

In total, of the 43 patients, 32 (74%) have progressed so far, and 26 (60.5%) have died (24 patients died from the disease and two patients died from pulmonary infection).

Induction chemotherapy with gemcitabine and paclitaxel showed a very favorable toxicity profile. Apart from one grade 4, allergic reaction to paclitaxel no significant toxicity was observed. Two of the patients were hospitalized due to febrile neutropenia. The acute toxicities of concurrent chemoradiotherapy with paclitaxel were acceptable. Severe oesophagitis and pneumonitis were uncommon in our study patients, although they have been dose limiting in other trials (21). Only 6% of the patients experienced grade 3 oesophagitis and only grade 2, pneumonitis occurred.

Although in our study 69% of the patients completed at least 4 weeks of paclitaxel and 50 Gy of radiotherapy, 7 patients (22%) received less than 50 Gy of radiotherapy. This could explain the lower incidence of oesophagitis and pneumonitis compared to other trials. The radiation doses were suboptimal and were related to poor tolerance by the patients.

Early studies, in which standard radiotherapy was combined with full doses of gemcitabine, resulted in unacceptable pulmonary and esophageal toxicities (22, 23). When radiotherapy is used concurrently with paclitaxel and carboplatin, the rate of Grade 3 or 4 esophageal toxicity has been reported to be approximately 25% (24).

Oesophagitis was consistently the main adverse event in three Phase II studies evaluating concurrent radiotherapy and docetaxel monotherapy in patients with unresectable NSCLC (25-27). Another cause of concern was the unpredictable occurrence of pulmonary toxicity, which occurred in two of the three studies (26, 27).

Concurrent chemoradiotherapy with paclitaxel, following induction chemotherapy with paclitaxel and gemcitabine, is feasible for the treatment of stage III NSCLC with reasonable efficacy and acceptable toxicity.

Conflict of Interest

None of the co-authors has any financial or personal relationship with other people or organizations that could inappropriately influence this work.

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