A phase II study of induction chemotherapy followed by concurrent chemoradiotherapy in elderly patients with locally advanced non-small-cell lung cancer

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The optimal management of unresectable locally advanced non-small-cell lung cancer in older patients has not been defined to date. The present phase II study was planned to evaluate the activity and safety of platinum-based induction chemotherapy followed by concurrent chemoradiotherapy in elderly patients with locally advanced non-small-cell lung cancer. Patients received two cycles of paclitaxel (175 mg/m^2) and carboplatin (area under the curve: 5) day 1, every 3 weeks. Chemoradiotherapy (thoracic radiation therapy) was initiated on day 42 and consisted of 1.8 Gy daily, five times per week over 5 weeks (45.0 Gy target dose) followed by 10 2.0 Gy daily fractions. Concomitant chemotherapy was weekly paclitaxel 50 mg/mq followed by weekly carboplatin at an area under the curve of 2. The eligibility for patients: age 70 or older and histologically documented untreated non-small-cell lung cancer, locally advanced, unresectable, stage III A N2 bulky or III B. Thirty consecutive patients were enrolled onto the study. The median age was 73 (range 70–76). According to the intention-to-treat analysis, 1 month after the end of combined chemoradiotherapy, we observed complete and partial responses in one and 19 of the 30 patients, respectively, for an overall response rate of 66% (95% confidence interval, 45–76%). Median progression-free survival was 8.7 months (95% confidence interval, 3.4–37.8) and median survival was 15 months (95% confidence interval, 4.2–52.1). During the treatment, 12 patients (40.0%) experienced grade 3–4 neutropenia, two patients neutropenic fever, and three patients grade 3 anaemia and grade 3 thrombocytopenia, respectively. Grade 3 oesophagitis, during concomitant radiotherapy, was observed in six patients (20.0%). No treatment-related mortality was reported. The investigated sequential approach including induction chemotherapy followed by concurrent chemoradiotherapy appears safe and seems a reasonable chance for the treatment of locally advanced non-small-cell lung cancer in the elderly population.
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Introduction

Lung cancer is the leading cause of tumour-related deaths in the elderly population [1]. The majority of primary lung cancers, approximately 80%, are of non-small-cell histology. The optimal management of unresectable locally advanced non-small-cell lung cancer (NSCLC) in older patients has not been defined to date. Reduced organ function, concomitant morbidities, increased medication usage, delayed diagnosis and physician's perception constitute barriers to enrolment of elderly cancer patients in clinical trials [2]. Patients aged more than 70 years accounted for most of the under-representation. Excluding all trials of hormonal therapy for breast cancer, the overall enrolment of patients aged 65, 70 and $\geq$ 75 years decreased to 25, 12 and 4%, as compared with 60, 46 and 31%, respectively, for the corresponding age group in the US cancer population [3]. It has long been assumed that chemotherapy is too toxic and of marginal benefit for elderly NSCLC patients and those with a performance status (PS) of 2. Up to the mid-1980s, the standard treatment for locally advanced NSCLC was thoracic radiation therapy (TRT), but the

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results were disappointing, with a median survival time of less than 1 year and long-term survival rates of 3–7% [4]. Both locally and distant failure were significant problems, as 70% of patients failed at distant sites and less than 20% achieved durable local control. In trials comparing cisplatin-based chemotherapy and radiotherapy to radiotherapy alone, the combined treatment arm was superior to radiotherapy alone [5–7]. Furthermore, concurrent administration of both chemotherapy and radiotherapy was superior to induction chemotherapy followed by radiotherapy alone [8–10]. The percentage of patients 70 years old or older in these studies, however, is small, ranging from 17 to 26% [8–10]. Very few specific prospective trials on the treatment of locally advanced NSCLC in the elderly population have been published. Some phase II studies suggest that low-dose chemotherapy given together with radiotherapy may be safely administered to this patient population [11]. The analysis of retrospective analyses on full-dose sequential and concurrent chemoradiation is subject to several methodological and selection biases [11]. Furthermore, none of these trials evaluated comorbidity as a prognostic factor [11]. Only specifically designed prospective studies can value the real role and feasibility of combined chemoradiotherapy in the treatment of locally advanced NSCLC in the elderly patients. The present monoinstitutional phase II study was planned to evaluate the activity and toxicity of platinum-based induction chemotherapy followed by concurrent chemoradiotherapy as scheduled treatment of elderly patients with locally advanced unresectable NSCLC.

Patients and methods

Study design, efficacy evaluations and statistical considerations

The study was a phase II trial. The primary endpoint was response rate; the secondary endpoints were treatment toxicity, time to treatment failure and survival obtained by carboplatin and paclitaxel-based induction chemotherapy followed by concurrent chemoradiotherapy for the treatment of locally advanced NSCLC elderly patients. Tumour response was evaluated by computed tomography (CT) scan according to standard World Health Organization criteria [12] after two cycles of chemotherapy and 1 month after the end of combined chemoradiotherapy unless suspected early progression of disease. Positron emission tomography (PET) was also employed for assessment response of treatment. Survival was recorded from the day of registration to death or to the date of last follow-up or the date of point of the study if the patient was still alive at this time. The overall survival was estimated using the Kaplan–Meyer technique. The time to treatment failure was recorded from the day of registration to the date of first documented progressive disease (PD) or the date of death regardless of its course or to the date of point if no PD and no death appeared at this time. All results presented are based on eligible patients. According to the intention-to-treat principle, all patients enrolled were included in the analysis of treatment administration. The two-stage design proposed by Simon [13] was used for the study, with the assumption that a response rate of less than 40% would not warrant further study and a response rate of 50% or greater would be considered promising for further study of this regimen. In the first stage, 10 assessable patients were entered. If less than four responses were observed, accrual would stop with the conclusion that the regimen did not hold promise for further study. If five or more responses were observed, an additional 20 patients would be accrued in the second stage of the study.

Patient selection

Patients eligible for enrolment were men or women of the age 70 years or older and histologically documented NSCLC, locally advanced, unresectable, stage III A N2 bulky (ipsilateral mediastinal lymph nodes > 2 cm in short-axis diameter at CT) or III B and no previous surgical resection, chemotherapy or TRT. Mediastinoscopy or transbronchial needle aspiration was required for pathologically documented N2 or N3 disease. Histology could include squamous cell carcinoma, adenocarcinoma (including bronchoalveolar cell), large-cell anaplastic carcinoma (including giant and clear-cell carcinomas) or poorly differentiated NSCLC. Patients with malignant pleural/pericardial effusion or metastases to controlateral sopraclavicular lymph nodes or operable stage III B (cT4-N0–1 for invasion of tracheal carina or multiple nodules in only one lobe) were excluded. Patients with T4 N0–1 superior sulcus tumours eligible for trimodality therapy were also excluded. Patients also required having measurable disease and an Eastern Cooperative Oncology Group (ECOG) PS 0–1. Adequate haematological, hepatic and renal function were required. Adequate pulmonary function with forced expiratory volume (FEV) in 1 s > 900 ml and partial oxygen pressure $> 50\%$ were mandatory. The evaluation of Cardiovascular Health Study [14] and the Vulnerable Elderly Survey [15] score were adopted: only fit (Cardiovascular Health Study) patients with a Vulnerable Elderly Survey score < 4 were enrolled. The Charlson index was employed as comorbid illness scale [16]. The overall score is based on weights, ranging from 1 to 6, which are assigned to 19 selected conditions. Lung cancer was not taken into account in this calculation. Patients with a Charlson index score > 1 or 1 for chronic obstructive pulmonary disease with FEV 1 $< 50\%$ of the predict value were excluded. Patients with prior history of malignancy were excluded, except for carcinoma *in situ* of the cervix or breast and nonmelanoma skin cancer. Written informed consent had to be obtained from all patients.

Treatment plan

For the chemotherapy induction regimen, the patients received 175 mg/m^2 of intravenous paclitaxel over 3 h in

an outpatient setting. Immediately following the paclitaxel infusion, the patients received 5 area under the curve (AUC) of carboplatin, delivered as an intravenous infusion over 30 min. The same regimen of paclitaxel and carboplatin was repeated 3 × weeks later on chemotherapy day 22. The dose of carboplatin was calculated according to the Calvert formula [17] with glomerular filtration rate calculated using the Cockroft–Gault formula [18]. All patients were to receive two treatment cycles as induction chemotherapy. All chemotherapy dosing was based on the patient's actual weight. No dose escalation was allowed. Standard premedication before paclitaxel treatment was given consisting of dexamethasone 8 mg intravenously, chlorpheniramine 10 mg intramuscular and ranitidine 50 mg intravenously. Patients routinely received antiemetic prophylaxis with a serotonine antagonist. TRT was initiated on day 42 and consisted of 1.8 Gy daily, five times per week over 5 weeks (45.0 Gy target dose) followed by 10 2.0 Gy daily fractions (total dose of 65.0 Gy in 35 fractions over 7 weeks). The target volume included the post-induction chemotherapy volume of primary tumour, homolateral hilar and mediastinal nodes, and 1.5 cm margin. Not elective nodal irradiations were adopted. Radiotherapy was delivered with photon beams generated by a linear accelerator. PET was routinely employed for target volume and radiotherapy-treatment planning. The threshold dose model for predicting radiation pneumonitis were employed. The latter relates the volume of lung receiving more than 20 Gy (V 20) to the risk for developing radiation pneumonitis with greater risk when V 20 is superior to 25% [19]. Concurrent chemotherapy was administered with weekly paclitaxel 50 mg/mq as intravenous infusion over 1 h followed by weekly carboplatin at an AUC of 2 mg/ml-min administered over 30 min.

Dose delay and modifications

Each 21-day chemotherapy cycle could only be started if the absolute neutrophil count (ANC) and platelet counts on the day of treatment were at least 1500 and 100 000/ml, respectively. Treatment was delayed until this level was achieved. If the delay was greater than 2 weeks, the patient was taken off the study. If the ANC was < 500/ml or platelet count $< 50\,000$/ml at any point during the cycle, or febrile neutropenia, chemotherapy was administered at 75% of the planned dose. Patients came off the study for grade 3 or 4 neurotoxicity or symptomatic arrhythmia or atroventricular block. Paclitaxel was administered at 50% of the planned dose in the event of persistent grade 2 neurotoxicity. Two 21-day cycles of chemotherapy were administered unless PD or intolerable toxicity was recorded. During concurrent chemoradiotherapy, chemotherapy dose was reduced by 50% if the granulocyte count dropped from 1000 to 1490/ml or the platelet count dropped to 75 000 to 99 000/ml. Whether the granulocyte count dropped to less than 1000/ml or the platelet count dropped to less than 75 000/ml, the chemotherapy administration was omitted. TRT interruptions were allowed for grade 3–4 oesophagitis/mucositis, grade 3–4 neutropenia and grade 3–4 thrombocytopenia.

Patient evaluation

Pretreatment evaluations included a complete history, physical examination, complete blood cell count with differential, serum biochemistry, bronchoscopy, CT scan of the brain, chest and upper abdomen, radionuclide bone scan, PET, and electrocardiogram. PET was routinely employed for staging (patients with clinical N2 or N3 and negative mediastinum were excluded as patients with otherwise undetected extrathoracic metastatic disease). Tumour response was evaluated by CT scan after two cycles of chemotherapy and 1 month after the end of combined chemoradiotherapy unless suspected early progression of disease. PET also was employed for assessment of tumour response. Before each administration of chemotherapy, patients underwent a clinical examination, a routine biochemistry workup and blood cell counts. Safety parameters were assessed throughout the induction chemotherapy, chemotherapy/TRT treatment and during the follow-up period until 2 years after the date of enrolment. During follow-up, TAC and PET were included every 6 months (every 4 months for the first year) unless suspect progression of disease. Safety was assessed through monitoring treatment-emergent adverse events/toxicities (from induction chemotherapy and Chemotherapy/TRT treatments), and changes in clinical laboratory parameters, SpO_2, vital signs and physical examinations. For each patient and each type of toxicity, the worst degree of toxicity experienced throughout the treatment was used for the analysis. All toxicities were coded according to the National Cancer Institute Common Toxicity Criteria Version 2 [20].

Results

Patient characteristics

From January 2002 to January 2006, 30 consecutive patients were enrolled onto the study. The median age was 73 (range 70–76). Forty percent of the patients had stage III A bulky and 50% had a PS of 0. The distribution of the Charlson index score was 0 in six patients (20.0%) and one in 24 patients (80%). Of the patients with Charlson index score of 1 the distribution of comorbidities was the following: chronic obstructive pulmonary disease (without FEV 1 $< 50\%$ of the predict value or 900 ml or partial oxygen pressure $< 50\%$) in 18 patients, liver disease in two patients and diabetes in four patients. The characteristics of the 30 eligible patients are listed in Table 1.

Treatment administration

Twenty-seven patients received the planned two cycles of induction chemotherapy. The reason for not completing induction chemotherapy was patient refusal for

neutropenic fever (two patients) and diarrhoea (one patient). During the concurrent chemoradiotherapy, 60% of patients received all the programmed cycles of chemotherapy. The reasons for not completing the seven cycles of concurrent chemotherapy were progressive decreasing of ECOG PS (two patients) and treatment-related complications: haematological toxicity (five patients) and oesophagitis (five patients). The percentage of patients who completed the planned radiotherapy was 80%. The reasons of failure to complete the planned radiotherapy were treatment-related complications (oesophagitis) in five patients and poor health in one patient. No treatment-related deaths were observed.

Haematological toxicity

During the treatment 12 patients (40.0%) experienced grade 3–4 neutropenia (nine during concomitant treatment, with only two patients developing neutropenic fever) (Table 2). Three cases of grade 3 anaemia and three cases of grade 3 thrombocytopenia were observed during concomitant chemoradiotherapy.

Table 1 Patient characteristics

Characteristics	Number of patients (%)
Total number	30 (100)
Male/female	24/6 (80.0/20.0)
Age (years)	
Median	73
Range	70–76
Performance status	
Median	0
Range	0–1
Tumour differentiation	
Well differentiated	0
Moderately differentiated	19
Poorly differentiated or undifferentiated	11
Stage	
III A bulky	12
III B	18
Histology	
Squamous	19
Nonsquamous	11
Charlson index score	
0	6
1	24

Nonhaematological toxicity

Grade 3 or 4 toxicity was uncommon apart alopecia (Table 2). One patient experienced grade 3 neuropathy. Grade 3 oesophagitis, during concomitant radiotherapy, was observed in six patients (20.0%). During induction treatment, grade 3 nausea/vomiting was reported in four patients (13.3%) and grade 3 diarrhoea in two patients (6.6%). No acute radiation pneumonitis or grade 3 or 4 cardiac toxicity was observed.

Response and survival

According to the investigators assessments (Table 3), 1 month after the end of combined chemoradiotherapy, complete and partial responses were achieved by one and 19 of the 30 patients, respectively, for an overall response rate of 66.6% [95% confidence interval (CI), 45–76]. In addition, stable disease (SD) was observed in four (13.3%) patients and PD in six (20%) patients. The response assessed with PET was complete and partial in five and 16 patients, respectively. Furthermore, SD was observed in three patients and PD in six patients. Progression was local (one patient) and systemic (five patients with 2/5 with brain progression). The metabolic response after induction chemotherapy correlates well with decrease of tumour size as assessed by standard criteria, but more patients were judged as complete responder after chemoradiotherapy by PET (five patients) than by CT scan (one patient). The objective response after two cycles of induction chemotherapy was the following: partial response (PR) and SD were observed in 19 and five patients, respectively, PD in three patients. Response was also assessed after one cycle of induction chemotherapy in three patients (who refused to completing the planning induction chemotherapy) and SD were achieved by all patients. Survival analysis was performed in April 2006, after a median follow-up of 42 months. The median survival was 15

Table 2 Safety profile (according to NCI/CTC criteria)

	Number of patients with toxicity (%)				
Side effects	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Haematological					
Anaemia	4 (13.3)	3 (10)	3 (10)	0	10 (33.3)
Leucopenia	5 (16.6)	4 (13.3)	15(50)	3 (10)	27 (90.0)
Neutropenia	7 (23.3)	5 (16.6)	9 (30)	3 (10)	24 (80.0)
Thrombocytopenia	5 (16.6)	4 (13.3)	3 (10)	0	12 (40.0)
Nonhaematological					
Nausea/vomiting	5 (16.6)	4 (13.3)	4 (13.3)	0	12 (40.0)
Mucositis	3 (10)	4 (13.3)	3 (10)	0	10 (33.3)
Neurotoxicity	5 (16.6)	2 (6.6)	1 (3.3)	0	8 (26.6)
Diarrhoea	4 (13.3)	2 (6.6)	2 (6.6)	0	8 (26.6)
Asthenia	6 (20.0)	4 (13.3)	3 (10)	0	13 (43.3)
Myalgia/arthralgia	4 (13.3)	2 (6.6)	3 (10)	0	9 (30)
Esophagitis	5 (16.6)	5 (16.6)	6 (20)	0	16 (53.3)

NCI/CTC, National Cancer Institute Common Toxicity Criteria.

Table 3 Efficacy analysis in elderly advanced NSCLC patients

Objective responses	Number (%)	Overall response rate (%)	Overall tumour control rate (%)
Complete response	1 (3.3)	20 (66.6)	
Partial response	19 (63.3)		26 (86.6)
Stable disease	6 (20)		
Disease progression	4 (13.3)		
3-Year survival rates	20%		
95% CI	(11.4–27.6)		
Progression-free survival			
Median	8.7 months		
(95% CI)	(3.4–37.8)		
Overall survival			
Median	15 months		
(95% CI)	(4.2–52.1)		

CI, confidence interval.

months (95% CI, 4.2–52.1). The 3-year survival rate was 20% (95% CI, 11.4–27.6%). Median progression-free survival was 8.7 months (95% CI, 3.4–37.8). Of the 22 patients who progressed during follow-up, progression was only local in two patients, locale distant 12 (lung, liver and bone) and only distant in eight patients (lung, liver, brain, adrenal glands and bone). The salvage treatment at progression was gemcitabine (eight patients), pemetrexed (four patients), weekly paclitaxel (four patients), gefinitib (four patients) and erlotinib (two patients).

Discussion

Advancing age is associated with increased incidence of cancer and an increase in other age-related medical problems. Lung cancer is now the most common cause of cancer-related death for elderly population for both men and women. Approximately 30% of patients with NSCLC have unresectable locally advanced disease at diagnosis. The treatment of stage III NSCLC has evolved with combined-modality therapy, the current standard of care [7–9,21]. Furthermore, concurrent administration of both chemotherapy and radiotherapy was superior to induction chemotherapy followed by radiotherapy alone [8–10] and immediate combined-modality therapy appeared to have a greater appeal for treatment of locally advanced NSCLC [8–10,22,23]. Last, in the randomized phase II Locally Advanced Multi-Modality Protocol (induction chemotherapy followed radiotherapy versus induction chemotherapy followed concurrent chemoradiotherapy versus immediate concurrent chemoradiotherapy followed by consolidation chemotherapy), Belani *et al.* showed that concurrent weekly paclitaxel, carboplatin and radiotherapy followed by consolidation chemotherapy seems to be associated with the best outcome, but with greater toxicity [24]. Today, although the optimal treatment of locally advanced NSCLC has yet to be defined, immediate concurrent chemoradiotherapy followed by consolidation chemotherapy appear the most efficacious regimen for patients younger than 70 years, with ECOG PS 0–1 and minimal weight loss. Although this treatment appears to be associated with the best outcome, this schedule was associated with greater toxicity. The question arises whether this is also true for elderly patients with locally advanced NSCLC. Multimodality therapy is not frequently offered to those patients. The percentage of patients 70 years or older in most of these studies ranges from 17 to 26% [8–10]. It is important to determine whether elderly patients benefit from and tolerate combined-modality therapy as much as their younger counterparts. Lung cancer is a disease of the elderly and as age increases the probability of developing comorbid medical illness increases. Particularly, heart-related conditions and chronic obstructive pulmonary disease were recorded as a current problem as a part of medical history of the older patients. Underlying comorbid illness may preclude the safe administration of aggressive therapy and has independent prognostic significance for patients with lung cancer. It is necessary to account for comorbid illness when evaluating age as a potential prognostic factor. Reports are conflicting regarding the influence of age on the outcome of patients and the role of aggressive therapy in NSCLC locally advanced patients with unfavourable characteristics is controversial. Hayakawa, evaluating the results of elderly patients treated with high-dose radiation therapy for inoperable NSCLC, recommended definitive radiotherapy without chemotherapy, but a phase II study of the Southwest Oncology Group suggest, that patients with poor-risk features can tolerate and derive significant benefit from aggressive therapy [25,26]. Patients eligible for the Southwest Oncology Group phase II study had been excluded from cisplatin-based protocols because of poor pulmonary or renal function, congestive heart failure, hearing loss, peripheral neuropathy, or weight loss. Carboplatin, etoposide and concurrent TRT has been evaluated. Thirty of the 60 enrolled patients were between ages 66 and 79. The median overall survival was 13 months. No treatment-related deaths were observed. The most common grade 3 and 4 toxicities included leucopenia (50%), thrombocytopenia (23%) and oesophagitis (15%). Indeed, the chemoradiotherapy treatment in the poor-risk patients yielded a median overall survival similar to good-risk patients who received cisplatin-based chemoradiotherapy.

The studies which provided retrospective subgroup analyses for age as a prognostic factor in patients treated in radiotherapy/CHT trials could not identify age as a negative prognostic factor in multivariate analyses [8,27–29]. Furthermore, in the analysis of the North Central Cancer Treatment Group trial, survival rates of locally advanced NSCLC patients treated with concurrent chemoradiotherapy were equivalent for patients 70 years or older and younger patients, although patients 70 years older experienced more grade 4 haematological toxicity and pneumonitis [30]. Analysis of Radiation Therapy Oncology Group (RTOG), however, suggest that 70 years

or older patients achieved the best quality-adjusted survival with standard radiotherapy alone [31,32]. Similarly, in the phase III Intergroup trial comparing standard radiotherapy, standard radiotherapy with concomitant cisplatin and vinblastine and hyper-fractionated radiotherapy, for patients over age 70 years (66 of 490 enrolled patients), median survival on the radiotherapy arm (13.1 months) exceeded median survival in the concurrent chemoradiotherapy arm (10.9 months) [6]. Moreover, the RTOG 94-10 study showed that elderly patients had the best median survival with concurrent therapy [33]. The RTOG 94-10 compared sequential therapy with concurrent chemoradiotherapy and concurrent chemotherapy/hyper-fractionated radiotherapy. Eligibility was restricted to good-risk patients. Of the 610 patients enrolled, 104 were age 70 or older. Median survival in the elderly favoured concurrent chemotherapy-standard radiotherapy arm (22.4 versus 16.4 and 10.8 months in the sequential and concurrent chemotherapy/hyper-fractionated radiotherapy arm, respectively). The rate of grade 3–4 neutropenia and grade >3 oesophagitis was higher in older patients. Moreover, in the analysis by Rocha-Lima of the CALGB 9130 trial, the outcome was equivalent for patients 70 years or older and younger counterparts [34]. Last, in a recent meta-analysis of concurrent modality therapy based on platinum compounds, concomitant chemoradiotherapy appeared to have a differential effect on survival according to age, with the greater benefit for older patients [35]. In summary, there is conflicting data regarding the utility of aggressive combined-modality treatment in elderly patients with advanced NSCLC. Survival benefit can be achieved, but at the expense of increase in toxicity. These studies suggest that appropriately selected fit patients should be treated similarly to fit young patients. Older patients had similar local control and survival as younger patients, but experienced more myelosuppression and non-haematological toxicity (more pneumonitis on the North Central Cancer Treatment Group trial, more oesophagitis in the RTOG 9410 trial and more renal complications in the CALGB 9130 trial). There is a need to conduct phase III trials in locally advanced NSCLC specifically targeting the elderly, but, until such studies are conducted, elderly locally advanced NSCLC patients with good PS and limited comorbidity may be treated with concurrent chemoradiotherapy. The present phase II study was to assess the antitumour activity and toxicity of platinum-based induction chemotherapy followed by concurrent chemoradiotherapy as treatment of locally advanced, unresectable, stage III A N2 bulky or III B NSCLC in elderly patients, with good functional status and low comorbidity index. We used paclitaxel and carboplatin for the proved efficacy in the treatment of NSCLC, and omitted cisplatin for the age of patients and the better integration with radiation therapy of carboplatin. No treatment-related mortality was reported. The observed 20% of grade 3 oesophagitis in this study is similar to that reported in the literature (15–20%) [36,37]. No grade 3/4 lung toxicity was reported. The apparently high incidence of reported severe neutropenia (40%) could be related to the high frequency (weekly) of blood count determination performed in the present trial during the concomitant radiochemotherapy phase. In this study, the combined-modality therapy appeared feasible for elderly patients with good PS and limited comorbid conditions.

During this study, an overall response of 66% and a median survival of 15 months were reported. These activity data are congruent with those reported by most studies of combined chemoradiotherapy in patients with locally advanced NSCLC younger than 70 years. The addiction of induction chemotherapy resulted in no survival advantage [23], but induction chemotherapy permitted that the TRT target was the postinduction tumour volume. As the impact of acute toxicity may be greater for elderly patients, limited field radiation, as in this trial, should be considered. Toxicity to the lungs and oesophagus can be decreased by limited irradiation without a negative impact on clinical activity. In conclusion, this study investigated the sequential approach including induction chemotherapy followed by concurrent chemoradiotherapy. This approach merits further evaluation in large phase III studies specifically designed for the elderly population with locally advanced NSCLC.

References

1 Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. *CA Cancer J Clin* 1999; **49**:8–31.

2 Lewis JH, Kilgore ML, Goldman DP, Trimble EL, Kaplan R, Montello MJ, *et al.* Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol* 2003; **21**:1383–1389.

3 Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. *J Clin Oncol* 2004; **22**:4626–4631.

4 Perez CA, Pajak TF, Rubin P, Simpson JR, Mohiuddin M, Brady LW, *et al.* Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. *Cancer* 1987; **59**:1874–1881.

5 Dillman RO, Herndon J, Seagren SL, Eaton WL Jr, Green MR. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of Cancer and Leukemia Group B (CALGB) 8433 trial. *J Natl Cancer Inst* 1996; **88**:1210–1215.

6 Sause WT, Scott C, Taylor S, Johnson D, Livingston R, Komaki R, *et al.* Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small cell lung cancer. *J Natl Cancer Inst* 1995; **87**:198–205.

7 Le Chevalier T, Arriagada R, Quoix E, Ruffie P, Martin M, Douillard JY, *et al.* Radiotherapy alone versus combined chemotherapy and radiotherapy in unresectable non-small cell lung carcinoma. *Lung Cancer* 1994; **10 (Suppl 1)** S239–S244.

8 Curran WJ, Scott CB, Langer CJ. Long-term benefit is observed in a phase III comparison of sequential versus concurrent chemoradiation for patients with unresected stage III NSCLC: RTOGroup (RTOG) 9410. *Proc Am Soc Clin Oncol* 2003; **22**:621 [abstract 2499].

9 Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, *et al.* Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small cell lung cancer. *J Clin Oncol* 1999; **17**:2692–2699.

10 Zatloukal P, Petruzelka L, Zemanova M, Havel L, Janku F, Judas L, *et al.* Concurrent versus sequential chemoradiotherapy with cisplatin and

vinorelbine in locally advanced non-small cell lung cancer: a randomized study. *Lung Cancer* 2004; **46**:87–98.
11 Gridelli C, Maione P, Rossi A, Ciardiello F, Raben D. Treatment of locally advanced non-small cell lung cancer in the elderly. *Curr Opin Oncol* 2005; **17**:130–134.
12 Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer (Phila)* 1981; **47**:207–214.
13 Simon R. Optimal two-stage designs for phase II clinical trials. *Controlled Clin Trials*. 1989; **10**:1–10.
14 Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; **56**:M146–M156.
15 Saliba D, Elliot M, Rubestein LZ, Solomon DH, Young RT, Kamberg CJ, *et al*. The vulnerable elders survey: a tool for identifying vulnerable older people in the community. *J Am Geriatr Soc* 2001; **49**:1691–1699.
16 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method for of classifying prognostic comorbidity in longitudinal series. Development and validation. *J Chronics Dis* 1987; **40**:373–383.
17 Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, *et al*. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989; **7**:1748–1756.
18 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**:31–41.
19 Graham MV, Purdy JA, Emami B, Harms W, Bosch W, Lockett MA, *et al*. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 2001; **51**:19–20.
20 National Cancer Institute. *Common toxicity criteria (CTC). Version 2.0*. Bethesda: National Cancer Institute; 1999.
21 Fournel P, Robinet G, Thomas P, Souquet PJ, Lena H, Vergnenegre A, *et al*. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-etienne d'Oncologie Thoracique–Groupe Francais de Pneumo-Cancérologie NPC 95 study. *J Clin Oncol* 2005; **23**:5910–5917.
22 Huber RM, Schmidit M, Lang S, Borgmeier A, Huber RM, Flentje M, *et al*. Induction chemotherapy and following simultaneous radio/chemotherapy versus induction chemotherapy and radiotherapy alone in inoperable NSCLC (stage IIIA/IIIB). *Proc Am Soc Clin Oncol* 2003; **22**:622 [abstract 2501].
23 Vokes EE, Herndon JE III, Kelley MY. Induction chemotherapy followed by concomitant chemoradiotherapy versus chemoradiotherapy alone for regionally advanced unresectable non-small cell lung cancer: initial analysis of a randomized phase III trial. *J Clin Oncol* 2004; **22**:14s [abstract 7005].
24 Belani CP, Choy H, Bonomi P, Scott C, Travis P, Haluschak J, *et al*. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol* 2005; **23**:5883–5891.
25 Hayakawa K, Mitsuhashi N, Katano S, Saito Y, Nakayama Y, Sakurai H, *et al*. High-dose radiation therapy for elderly patients with inoperable or unresectable non-small cell lung cancer. *Lung Cancer* 2001; **32**:81–88.
26 Lau DH, Crowley JJ, Gandara DR, Hazuka MB, Albain KS, Leigh B, *et al*. Southwest oncology group phase II trial of concurrent carboplatin, etoposide, and radiation for poor-risk stage III non-small-cell lung cancer. *J Clin Oncol* 1998; **16**:3078–3081.
27 Jeremic B, Shibamoto Y, Milicic B, Nikolic N, Dagovic A, Milisavljevic S, *et al*. Concurrent radiochemotherapy for patients with stage III non-small-cell lung cancer (NSCLC): long-term results of a phase II study. *Int J Radiat Oncol Biol Phys* 1998; **42**:1091–1096.
28 Schaake-Koning C, van den Bogaert W, Dalesio O, Festen J, Hoogenhout J, van Houtte P, *et al*. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med* 1992; **326**:524–530.
29 Clamon G, Herndon J, Cooper R, Chang AY, Rosenman J, Green MR, *et al*. Radiosensitization with carboplatin for patients with unresectable stage III non-small-cell lung cancer: a phase III trial of the Cancer and Leukemia Group B and the Eastern Cooperative Oncology Group. *J Clin Oncol* 1999; **17**:4–11.
30 Schild SE, Stella PJ, Geyer SM, Bonner JA, McGinnis WL, Mailliard JA, *et al*. The outcome of combined-modality therapy for stage III non-small cell lung cancer in the elderly. *J Clin Oncol* 2003; **21**:3201–3206.
31 Werner-Wasik M, Scott C, Cox JD, Sause WT, Byhardt RW, Asbell S, *et al*. Recursive partitioning analysis of 1999 Radiation Therapy Oncology Group (RTOG) patients with locally-advanced non-small-cell lung cancer (LA-NSCLC): identification of five groups with different survival. *Int J Radiat Oncol Biol Phys* 2000; **48**:1475–1482.
32 Movsas B, Scott C, Sause W, Byhardt R, Komaki R, Cox J, et al. The benefit of treatment intensification is age and histology-dependent in patients with locally advanced non-small cell lung cancer (NSCLC): a quality-adjusted survival analysis of Radiation Therapy Oncology Group (RTOG) chemoradiation studies. *Int J Radiat Oncol Biol Phys* 1999; **45**: 1143–1149.
33 Langer CJ, Hsu C, Curran WJ, Komaki R, Lee JS, Byhardt R, *et al*. Elderly patients with locally advanced non-small cell lung cancer benefit from combined modality therapy: secondary analysis of Radiation Therapy Oncology Group (RTOG 9410). *Proc Am Soc Clin Oncol* 2002; **21**:299a [abstract 1193].
34 Rocha Lima CM, Herndon JE II, Kosty M, Clamon G, Green MR. Therapy choices among older patients with lung carcinoma: an evaluation of two trials of the Cancer and Leukemia Group B. *Cancer* 2002; **94**: 181–187.
35 Auperin A, Le Pechoux C, Pignon JP, Koning C, Jeremic B, Clamon G, *et al*. Concomitant radio-chemotherapy based on platinum compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. *Ann Oncol* 2006; **17**:473–483.
36 Wei X, Liu HH, Tucker SL, Liao Z, Hu C, Mohan R, *et al*. Risk factors for acute esophagitis in non-small-cell lung cancer patients treated with concurrent chemotherapy and three-dimensional conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 2006; **66**:100–107.
37 Park BB, Park JO, Kim H, Ahn YC, Choi YS, Kim K, *et al*. Is trimodality approach better than bimodality in stage IIIA, N2 positive non-small cell lung cancer? *Lung Cancer* 2006; **53**:23–30.