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A phase II single-arm study of induction chemotherapy with cisplatin and gemcitabine followed by concurrent cisplatin and gemcitabine with thoracic radiation for unresectable locally advanced non-small cell lung cancer

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Abstract

Objectives: The aim of this study was to evaluate the efficacy and tolerability of the combination of cisplatin–gemcitabine with concurrent thoracic radiotherapy for locally advanced non-small cell lung cancer (LA-NSCLC).

Methods: This was a phase II, multicenter, open-label, single-arm trial in treatment-naïve patients with stage IIIA and IIIB LA-NSCLC. After three induction cycles with gemcitabine 1250 mg/m^2 plus cisplatin 80 mg/m^2, two concurrent chemoradiotherapy cycles with gemcitabine 300 mg/m^2, cisplatin 80 mg/m^2, and radiotherapy (63 Gy) were administered. The primary endpoint was response rate after induction chemotherapy followed by concurrent chemoradiotherapy. Secondary endpoints included time to progressive disease (TtPD), overall survival (OS), and safety.

Results: Overall, 49 patients (median age 63.4 years; 73.5% male; Karnofsky performance status scores of 80, 85, 90, and 100 [16.3%, 2.0%, 49.0%, and 32.7%, respectively]; disease stage IIIA or IIIB 28.6% and 71.4%, respectively) were enrolled and treated. Response rate was 38.8% (95% confidence interval [CI] 25.2–53.8%). Median TtPD was 11.4 months (95% CI 9.4–12.9). Median OS was 21.8 months (95% CI 17.5–26.0), with 1- and 2-year survival rates of 70.8% and 43.7%, respectively. Overall, six patients discontinued from study treatment due to adverse events (AEs), of which two were serious AEs. The most relevant grade 3/4 AEs were neutropenia and thrombocytopenia in induction chemotherapy and chemoradiotherapy, and grade 3 events related to radiation in acute chemoradiotherapy, e.g. dysphagia, radiation pneumonitis, and radiation esophagitis.

Conclusions: Induction chemotherapy followed by concurrent chemoradiotherapy with gemcitabine (300 mg/m^2) and cisplatin was associated with acceptable toxicity. The observed median OS time was 21.8 months. Response evaluation was difficult as in many cases it was not possible to differentiate tumor progression from local radiofibrosis.

Keywords: concurrent chemoradiotherapy, gemcitabine, LA-NSCLC

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Introduction

One third of non-small cell lung cancer (NSCLC) patients present with stage III disease and are potentially eligible for curative chemoradiotherapy followed, or not, by surgery.

Chemotherapy may play a cytotoxic role by eradicating distant micrometastases and/or a radiosensitizing role by improving local control and reducing local/regional or distant relapse. The challenge is to find the regimen which best establishes local control and eradication of the distant micrometastases, while avoiding excessive toxicity.

Meta-analyses investigating the benefit of administering chemotherapy either concurrently or sequentially with radiation demonstrated that concurrent chemoradiotherapy produced improved survival for appropriately selected patients compared with radiotherapy alone [Non-small Cell Lung Cancer Collaborative Group, 1995] and sequential chemoradiotherapy [Aupérin *et al.* 2006; Fournel *et al.* 2006; Garrido *et al.* 2009; Berghmans *et al.* 2009]. Another meta-analysis also showed improved survival with concurrent chemoradiotherapy as compared with sequential chemoradiotherapy (hazard ratio = 0.84; $p = 0.004$) [Aupérin *et al.* 2010]. Absolute improvement in survival was 5.7% at 3 years (23.8% *versus* 18.1%) and 4.5% at 5 years (15.1% *versus* 10.6%). No difference was seen in pulmonary toxicity, but the relative risk of grade 3/4 acute esophagitis was higher in the concurrent group (relative risk = 4.9; $p < 0.0001$).

In 2002, Vokes and colleagues from the Cancer and Leukemia Group B [Vokes *et al.* 2002a] reported the results of a randomized phase II trial (CALGB 9431 Trial) of treatment-naïve patients with unresectable stage III NSCLC. The three-arm study evaluated induction chemotherapy (arm 1: gemcitabine with cisplatin; arm 2: paclitaxel with cisplatin; and arm 3: vinorelbine with cisplatin) followed by chemoradiotherapy. A statistical comparison among the arms was not possible because of the study design, nevertheless median survival times for arms 1, 2, and 3 (18.3, 14.8, and 17.7 months, respectively) were clinically comparable as were response rates (74%, 67%, and 73%, respectively), with gemcitabine having a numerically higher 3-year survival rate (28% *versus* 19% and 23%, respectively). The different toxicity profiles of the three concurrent chemoradiotherapy arms were evaluated and it was shown that grade 3/4 esophagitis (35%/17%) was indeed most common with gemcitabine, however radiation pneumonitis was not. Despite the dose reduction of gemcitabine from the full systemic dose of 1250 mg/m^2 to the concurrent chemoradiotherapy dose of 600 mg/m^2, toxicity was still high.

Gemcitabine is a potent radiosensitizer with a safety profile comparable to third-generation agents when used concurrently with radiotherapy. The full dose of gemcitabine can lead to fatal toxicity; therefore, the dose should be adequately reduced during concurrent chemoradiotherapy. A dose of 350 mg/m^2 was shown to be optimal in combination with radiation therapy [Trodella *et al.* 2002].

We postulated that by adding one cycle of systemic chemotherapy in the induction phase and reducing the gemcitabine dose from 600 to 300 mg/m^2 during concurrent chemoradiotherapy, tolerability could be improved, and efficacy should not be compromised compared with the approach used in the CALGB 9431 Trial.

The present study thus aimed to evaluate whether combining three cycles of cisplatin–gemcitabine (at 1250 mg/m^2) induction chemotherapy followed by two cycles of cisplatin–gemcitabine (at 300 mg/m^2) during standard thoracic radiotherapy is feasible without compromising efficacy. The primary objective was to assess the response rate after induction chemotherapy followed by concurrent chemoradiotherapy. Secondary objectives were to determine time to progressive disease (TtPD) and overall survival (OS) (median survival; 1- and 2-year survival) and to evaluate the safety of induction chemotherapy and chemoradiotherapy.

Patients and methods

This multicenter, open-label, single-arm, phase II trial [ClinicalTrials.gov Identifier: NCT00192036] was conducted at eight study centers in Belgium from August 2004 to November 2009 to evaluate the efficacy and tolerability of the combination of cisplatin–gemcitabine with concurrent thoracic radiotherapy for locally advanced (LA) NSCLC. The study was reviewed and approved by an ethical review board at each participating institution and was performed in compliance with the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki. All patients and/or their authorized legal representatives provided written informed consent prior to undergoing any study procedure or receiving any study drug.

Eligible patients were treatment-naïve, with a cytologically or histologically proven, clinical stage IIIA-IIIB NSCLC judged inoperable at diagnosis (staging based on computerized tomography [CT] scans only). All patients were ≥18 years of age with at least one measurable lesion (Response Evaluation Criteria in Solid Tumors [RECIST] 1.0 criteria [Therasse *et al.* 2000]), Karnofsky status 70–100 both at study entry and before starting chemoradiotherapy, estimated life expectancy of >12 weeks, lung function tests (forced expiratory volume in 1 second [FEV_1] or diffusing capacity of the lung for carbon monoxide [DLco]) ≥50% of normal, weight loss of <10% within the last 6 months, and no concurrent serious illness or medical conditions. Adequate hematological parameters and organ function were required.

Evaluations

Before enrollment, medical history was recorded, physical examination was performed, and Karnofsky performance status was assessed. Laboratory investigations included complete and differential blood counts and assays of electrolytes, glucose, calcium, albumin, transaminases, alkaline phosphatase, total bilirubin, and creatinine. An electrocardiogram was recorded. A bronchoscopy was performed. Lung function was assessed by FEV_1, forced vital capacity (FVC) and DLco. Also at baseline, all symptoms were recorded according to NCI Common Toxicity Criteria (CTC) Version 2.0 [NCI, 1999] and Early and Late Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) Toxicity Scales scoring [Cox *et al.* 1995].

Chemotherapy

Treatment was administered as a 21-day cycle (for five cycles, with gemcitabine given on days 1 and 8 and cisplatin given on day 1, concurrently with thoracic radiotherapy during the last 2 cycles). During induction chemotherapy (cycles 1–3), gemcitabine 1250 mg/m^2 was given intravenously (IV) over 30 minutes, followed by cisplatin 80 mg/m^2 infused over 60 minutes on day 1 and followed by hydration according to local practice. Appropriate antiemetic premedication was administered. During chemoradiotherapy (cycles 4 and 5), chemotherapy was administered in the same manner with gemcitabine reduced to 300 mg/m^2; chemotherapy was to be given at least 4 hours prior to radiotherapy on the days of concurrent administration.

During both induction chemotherapy and chemoradiotherapy, prior to each cycle, a physical examination, tumor measurements, hematology, chemistry, and toxicity assessments were performed. Hematology was also assessed on days 8 and 15 and toxicity was assessed on day 8. During chemoradiotherapy, a physical examination was also performed on day 8.

Any dose modifications were performed per the gemcitabine label.

Radiotherapy

Radiotherapy began within 7 days after the completion of induction chemotherapy (within 7 days from day 21 of the cycle 3). Total dose to the involved areas was 63 Gy in 35 fractions of 1.8 Gy each, for 5 days a week given over a period of 7 weeks. Total treatment time was less than 48 days.

A volumetric treatment planning CT study was required to define gross tumor volume (GTV) and planning target volume (PTV). Contiguous slices with a thickness of 3–5 mm were obtained from the level of the cricoid cartilage and extending inferiorly through the liver. The GTV, clinical target volume (CTV), PTV, and normal organs were outlined on all appropriate CT slices and displayed using beam's eye view. Normal tissues to be contoured included lung, heart, spinal cord, and esophageal tissues.

The GTV included the residual tumor volume after chemotherapy (minimally, the initially involved bronchus) as well as mediastinum and lymph nodes with a diameter larger than 1 cm as measured on the prechemotherapy CT scan. If a positron emission tomography (PET) scan was available, only PET-positive locations were included in the GTV. The CTV consisted of a 1 cm margin of normal tissue around the GTV.

The PTV consisted of an additional margin in the cranial–caudal direction of 0.7 cm to the CTV and in left–right and anterior–posterior directions of 0.5 cm to the CTV. Dose was specified according to ICRU50.

During the entire study, doses of chemotherapy and radiotherapy were reduced according to laboratory or clinical toxicity. NCI CTC Version 2.0 and Early and Late Radiation RTOG/EORTC Toxicity Scales were used.

Response evaluation

RECIST 1.0 was used for response evaluation. Tumor evaluation included documentation of measurable and nonmeasurable disease sites by physical examination, X-ray and CT scan, upper abdomen CT scan, and bone scan. Reviews of X-rays and CT scans were performed locally.

Response evaluation for the primary objective was performed at the first follow-up (FU) visit. At all FU visits, a physical examination and toxicity assessment were performed, and lung function and tumor evaluation were measured (during FU, a chest X-ray was to be done every visit; and a CT scan of the chest was to be done at every other FU visit). First FU visit was performed 6–8 weeks after the last day of radiotherapy; subsequent FU visits occurred every 3 months for the first 2 years and at least every 6 months thereafter.

Concomitant treatment

Patients received best supportive care while on study, but could not receive any other anticancer drugs, including immunotherapy and hormonal therapy (excluding contraceptives and steroids). Patients were not allowed to routinely receive colony-stimulating factors as primary prevention for febrile neutropenia.

Statistical methods

The study was originally designed to enroll 67 patients. This design would have given an 80% chance of correctly concluding that the regimen was worthy of further study if the true response rate was 55% and a 5% chance of incorrectly concluding that the regimen was worthy of further study if the true response rate was 40%. However, due to slow enrollment, the trial was stopped after 49 patients had been enrolled.

Descriptive statistics (e.g. mean, standard deviation, median, and range) were used to summarize quantitative variables. Frequencies and percentages were used to summarize qualitative variables. All CIs for parameters to be estimated were constructed using a two-sided, 5% significance level.

Efficacy variables were analyzed in the intent-to-treat population (ITT; all eligible patients that received at least one dose of study medication). The primary objective was to assess the response rate at the end of treatment (after induction chemotherapy followed by concurrent chemoradiotherapy). Response rate was determined by the ratio of complete and partial responders divided by the total number of enrolled patients. The 95% CI for the response rate was calculated using the normal approximation to the binomial distribution as described by Leemis and Trivedi [Leemis and Trivedi, 1996].

Secondary efficacy objectives included TtPD and OS (median survival; 1- and 2-year survival). TtPD was defined as the time from the date of enrollment to the first date of documented disease progression. For patients who were still alive at the time of analysis without disease progression, and for patients dying for reasons other than tumor progression, TtPD was censored at the date of the last FU visit. OS time was defined as the time from study enrollment to time of death due to any cause. For patients who were still alive at the time of the analysis, survival was censored at the date of the last FU visit.

TtPD and OS were estimated by using the Kaplan–Meier method [Kaplan and Meier 1958], including quartiles for each variable. The 1-, 2-, and 3-year survival rates along with 95% CIs were reported.

The ITT population was used for safety assessments, which included summaries of CTC grade 3 or 4 AEs, serious adverse events (SAEs), deaths, and study discontinuations due to AEs. AEs were analyzed globally and for the following three periods: (1) induction chemotherapy phase (cycles 1–3, from the start of the first infusion until the end of cycle 3); (2) acute chemoradiotherapy phase (cycles 4 and 5, from the start of chemoradiotherapy until 49 days after the end of chemoradiotherapy [first FU visit 49 days ± 7 days after the end of treatment]); and (3) late toxicities to chemoradiotherapy (from 49 days after the end of chemoradiotherapy until the end of the FU). Only AEs thought to be related to study drug were reported during this period.

Results

Patient disposition and patient characteristics at baseline

The study was planned to enroll 67 patients in approximately 27 months. Actual enrollment started in August 2004 and, due to difficulties with patient recruitment, was stopped prematurely in September 2007 after 49 patients had been enrolled. No new patients were included in the study after September 2007. The study was active until last patient visit occurred in November 2009 after 2-year FU.

Table 1. Baseline demographics and clinical characteristics of patients.

Total number of enrolled patients	49
Age, years, median (min/max)	63.4 (46.5/82.9)
Gender, males, *n* (%)	36 (73.5)
Karnofsky Performance Status, *n* (%)	
80	8 (16.3)
85	1 (2.0)
90	24 (49.0)
100	16 (32.7)
Disease stage, *n* (%)	
Stage IIIA	14 (28.6)
Stage IIIB	35 (71.4)
Pathological diagnosis, *n* (%)	
Histopathological	39 (79.6)
Cytological	10 (20.4)
Histology, *n* (%)	
Adenocarcinoma	18 (36.7)
Large cell	7 (14.3)
Other pathological diagnosis	2 (4.1)
Squamous cell	22 (44.9)

Overall, 49 patients (median age 63.4 years, 73.5% male) with Karnofsky performance status scores of 80, 85, 90, and 100 (16.3%, 2.0%, 49.0%, and 32.7%, respectively) were enrolled. Of these, 28.6% had disease stage IIIA and 71.4% had disease stage IIIB. Patient and disease characteristics at baseline are shown in Table 1. As shown in Figure 1, all enrolled patients were treated with at least one dose of study drug, 31 patients (63.3%) entered the concurrent chemoradiotherapy, and 28 patients (57.1%) completed the entire treatment period. A total of 21 patients (42.9%) discontinued during the study.

Doses administered

During treatment, the gemcitabine dose was adjusted in 24 patients (49.0%); 12 patients (24.5%) had dose reductions and 18 patients (36.7%) had dose delays for gemcitabine. The cisplatin dose was adjusted in 16 patients (32.7%). Six patients (12.2%) had dose reductions and 14 patients (28.6%) had dose delays for cisplatin.

Primary efficacy variable

Response rates after induction chemotherapy followed by concurrent chemoradiotherapy for the 49 enrolled patients is as follows: complete response (CR) was recorded in one patient (2.0%) and partial response (PR) was recorded in 18 patients (36.7%). Response rate (CR+PR) was 38.8% (95% CI 25.2–53.8%).

Stable disease (SD) was recorded in three patients (6.1%).

Progressive disease (PD) was confirmed for six patients (12.3%) of the ITT population, of which five patients (10.2%) discontinued due to disease progression before radiotherapy and one patient (2.0%) progressed during radiotherapy. For 21 patients (42.9%), status of response was considered as 'nonevaluable'. 'Nonevaluable' included those patients for whom there was no response assessment or the assessment took place after the patient had started taking a new therapy (and may include further unconfirmed SD or PD).

Secondary efficacy variables

TtPD and OS are shown in Figures 2 and 3 (all 49 enrolled patients). The median time to progression was 11.4 months (95% CI 9.4–12.9 months). A total of 11 patients (22.4%) were censored at the date of the last FU visit, with six patients still alive without documentation of PD, four patients died from reasons other than PD, and one patient was lost to FU. The proportion of subjects who had a TtPD of at least 12 months was 41.6% (95% CI 27.0–56.2%), and of at least 24 months was 18.5% (95% CI 6.9–30.0%).

Median OS time was 21.8 months (95% CI 17.5–26.0 months). The 1- and 2-year survival rates were 70.8% (95% CI 58.0–83.7%) and 43.7% (95% CI 29.7–57.8%), respectively; the 3-year survival rate was 28.8% (95% CI 15.9–41.7%). Of the 12 patients (24.5%) who were censored, 11 were still alive and 1 patient was lost to FU.

Safety and tolerability

Overall, six patients discontinued from study treatment due to AEs, of which two were SAEs.

The most relevant CTC grade 3/4 AEs were neutropenia (induction chemotherapy: grade 3, 18.4%; grade 4, 16.3% and acute chemoradiotherapy:

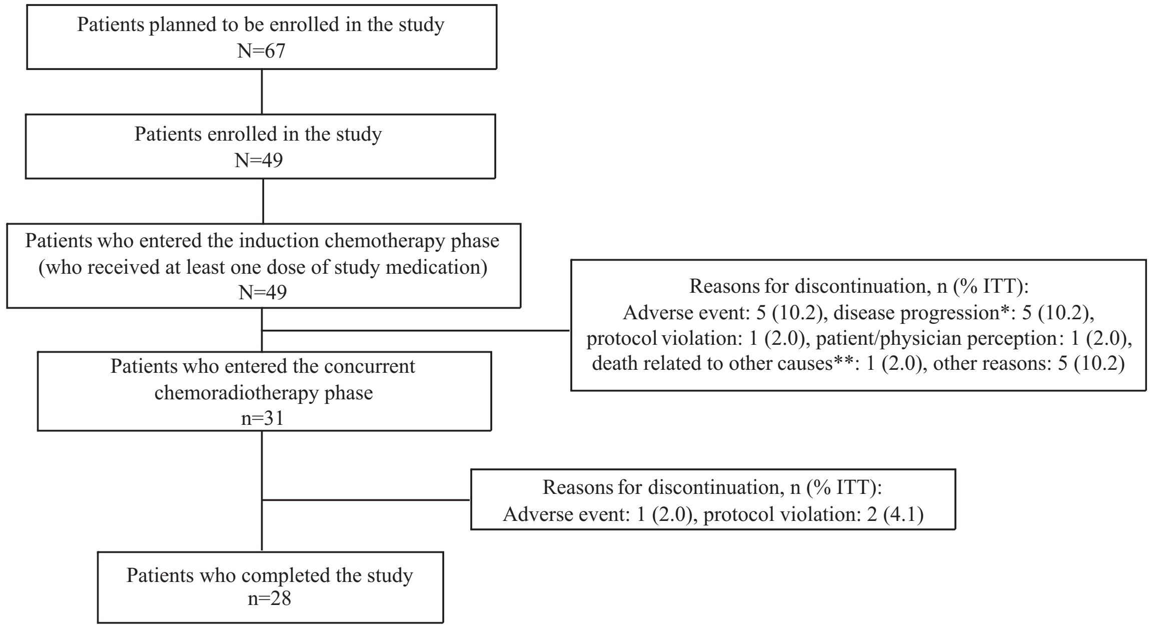

Figure 1. Patient disposition.
* Objective tumor progression: 4 (8.2), clinical deterioration: 1 (2.0).
** Neither related to study drug toxicity nor study disease.
ITT, Intent-to-Treat Population.

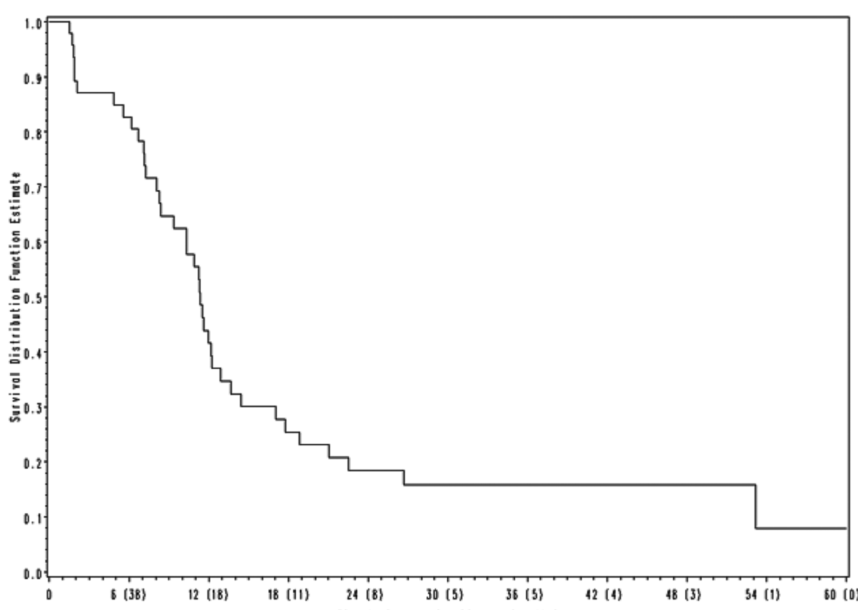

Figure 2. Kaplan–Meier curve for time to progression (enrolled patients).

grade 3, 19.4%; grade 4, 6.5%), thrombocytopenia (acute chemoradiotherapy: grade 3, 22.6%; grade 4, 3.2%), and grade 3 events related to radiation in acute chemoradiotherapy, e.g. dysphagia (6.5%), radiation pneumonitis (3.2%), and radiation esophagitis (12.9%).

A summary of all serious treatment-emergent AEs (TEAEs) and SAEs (during the late toxicities period) is given in Table 2.

The number of patients who experienced at least one SAE possibly related to either study drug or

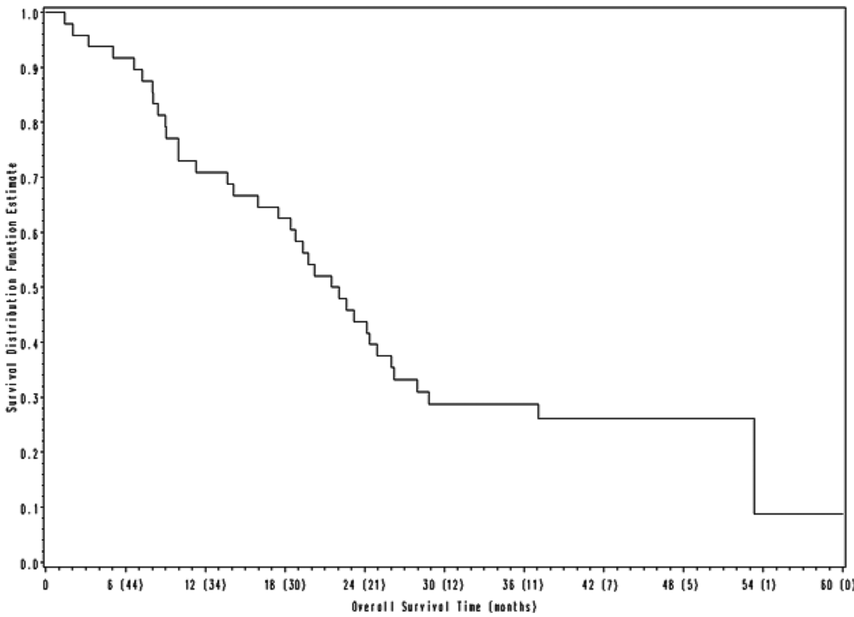

Figure 3. Kaplan–Meier curve for overall survival (Enrolled Patients).

radiation therapy was: three patients during induction chemotherapy, seven patients during the acute chemoradiation therapy and two patients during the late toxicity phase. A small number of serious TEAEs occurred during the induction chemotherapy phase (e.g. febrile neutropenia and renal failure, incidence 2%, respectively). The most common serious TEAEs during acute chemoradiotherapy included radiation esophagitis (12.9%) and radiation pneumonitis (6.5%). In the late toxicity phase, the highest incidence of SAEs was 3.2% (e.g. dysphagia).

There were 37 deaths during the study. One patient died in a car accident during study treatment; the other deaths occurred while the patients were in the FU period.

Discussion

The aim of the present study was to evaluate whether combining three cycles of cisplatin–gemcitabine (at 1250 mg/m^2) induction chemotherapy followed by two cycles of cisplatin–gemcitabine (at 300 mg/m^2) combined with standard thoracic radiotherapy is feasible without compromising efficacy.

Clinical trials were not able to demonstrate a clear benefit of induction or consolidation chemotherapy in addition to concurrent chemoradiotherapy. The LAMP phase II study demonstrated that concurrent chemoradiotherapy/consolidation chemotherapy treatment sequence appeared to be associated with the best outcome, though this schedule was associated with higher toxicity [Belani *et al.* 2005].

Consolidation strategy was investigated in a randomized phase III study [Hanna *et al.* 2008] that compared concurrent etoposide/cisplatin/radiation with or without consolidation docetaxel. The study was closed early as no difference in survival between the two arms was likely, and additional severe toxicity was seen in the docetaxel arm (e.g., increased hospitalizations and premature death, with grades 3–5 pneumonitis in 1.4% of patients in the observation arm and 9.6% of patients in the docetaxel arm).

The role of two cycles of induction carboplatin/paclitaxel before concurrent chemoradiotherapy with the same agents was evaluated in the CALGB 39801 trial [Vokes *et al.* 2002b]. Induction chemotherapy did not significantly improve median survival.

The most promising results were reported from a phase II trial examining etoposide/cisplatin with radiation, followed by docetaxel consolidation (SWOG 9504) in patients with stage IIIB disease [Gandara *et al.* 2006].

Table 2. Incidence of all serious TEAEs possibly related to either study treatment or radiotherapy (during treatment) and SAEs (during the late toxicities period).

	Induction chemotherapy phase, cycles 1–3 (*N* = 49) Serious TEAEs	Acute chemoradiotherapy phase, cycles 4 and 5 (*N* = 31) Serious TEAEs	Late toxicity phase, from 49 days after end of chemoradiotherapy until end of follow up (*N* = 31) SAEs
Patients with at least 1 serious (treatment-emergent) AE possibly related to either study	3 (6.1)	7 (22.6)	2 (6.5)
Febrile neutropenia	1 (2.0)	2 (6.5)	0
Neutropenia	0	2 (6.5)	0
Leukopenia	0	1 (3.2)	0
Thrombocytopenia	0	1 (3.2)	0
Radiation esophagitis	0	4 (12.9)	0
Radiation pneumonitis	0	2 (6.5)	0
Road traffic accident	1 (2.0)	0	0
Anorexia	0	2 (6.5)	0
Anxiety	0	1 (3.2)	0
Depressed mood	0	1 (3.2)	0
Dyspepsia	0		1 (3.2)
Dysphagia	0	1 (3.2)	1 (3.2)
Odynophagia	0	0	1 (3.2)
Esophagitis	0	1 (3.2)	0
Vomiting	0	1 (3.2)	1 (3.2)
Malaise	0	0	1 (3.2)
Hyperthermia	0	1 (3.2)	0
Renal failure	1 (2.0)	0	0
Weight decreased	0	0	1 (3.2)

Note: All data are *n* (%) unless otherwise specified.
AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

The present trial is a modification of the CALGB 9431 study. In the gemcitabine arm of the CALBG 9431 study, a dose of 1250 mg/m^2 gemcitabine was used in induction chemotherapy (for two cycles, with gemcitabine given on days 1 and 8, and cisplatin 80 mg/m^2 given on day 1). Full-dose chemotherapy may be required to reduce distant failure rates; however, during concurrent administration of thoracic irradiation, chemotherapy doses might need to be reduced because of toxicities such as esophagitis or pneumonitis [Zinner *et al.* 1999]. Therefore, the concurrent phase was reduced to 600 mg/m^2 gemcitabine on days 1 and 8, with cisplatin remaining unchanged for two cycles along with 2 Gy/day of radiation.

In the CALBG 9431 study, patients' disease-stage ratio was stage IIIA 63% and stage IIIB 37%. Efficacy results revealed a median survival of 18.3 months; 1- and 2-year survival was 68% and 37%, respectively. Best overall response was 74%. In terms of safety, neutropenia grade 3/4 was reported in 33% and 18% of patients, respectively, thrombocytopenia grade 3/4 in 33% and 23%, respectively, and radioesophagitis grade 3/4 in 35% and 17%, respectively.

The original intention of the present study as a modification of the CALBG 9431 study was to avoid excessive toxicity while achieving local control and eradicating distant micrometastases by reducing gemcitabine during radiotherapy and adding one cycle of full systemic chemotherapy. However, the results of these two studies are not comparable, mainly due to substantially different patient populations, different regimens, different primary efficacy variables, and different response assessments.

Compared with the CALGB 9431 study, the present study had broader patient entry criteria. The CALGB 9431 study excluded patients with a pretreatment weight loss of >5% in 3 months, while the present study allowed pretreatment weight loss of <10% over 6 months. In contrast with the present study, N3 patients with supraclavicular node involvement were excluded in the CALGB 9431 study.

In the present study, enrolled patients had a more advanced disease-stage ratio IIIA/IIIB of stage IIIA 29% and stage IIIB 71%.

Response rate was 38.8% in the ITT patients.

Median survival was 21.8 months; 1- and 2-year survival was 71% and 44%, respectively.

Most important toxicities during the chemoradiotherapy phase were neutropenia (grade 3, 19.4%; grade 4, 6.5%) and thrombocytopenia (grade 3, 22.6%; grade 4, 3.2%). Owing to the lower dose of gemcitabine during radiation, radioesophagitis was acceptable (grade 3, 12.9%, no grade 4 events).

Regarding the limitations of the present study, the study faced problems with patient recruitment. Enrollment was stopped prematurely when only 49 of 67 planned patients were included.

Response rate was used as primary efficacy criterion, but response rate was difficult to assess and 44.9% of the ITT patients (with 17.9% of protocol completers) had a nonevaluable response according to the narrow primary objective protocol definition. Per protocol, response rate according to RECIST was assessed only after induction chemotherapy followed by concurrent chemoradiotherapy. Moreover, there were local changes in the radiation field seen on the CT scan, in which case it was impossible for the investigator to differentiate between tumor progression and local radiofibrosis. This local fibrosis in the radiation field was a disturbing finding and troublesome for evaluating radiological tumor response, but it had no functional repercussion. Therefore, the assessment of response is an unreliable efficacy parameter for radiotherapy in NSCLC.

The primary efficacy criterion (response rate of 40% in ITT patients after induction chemotherapy followed by concurrent chemoradiotherapy) was not met. The above-mentioned issues with response rate evaluation might have contributed to this outcome.

In conclusion, despite the limitations of this study, induction chemotherapy followed by concurrent chemoradiotherapy with gemcitabine (300 mg/m^2) and cisplatin was associated with acceptable toxicity. The observed median OS time was 21.8 months.

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Conflict of interest statement

Dr Peter Driesen, Dr Marc Lambrechts, and Dr Benoit Colinet were investigators in the study. Dr Driesen stated that he received reimbursement for travel expenses related to the study. Dr Colinet and Dr Lambrechts have no other relevant financial interest in this publication. Kees Kraaij, Victoria Soldatenkova, and Nadia Chouaki are fulltime employees of Eli Lilly.

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