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Original Research

Induction or consolidation chemotherapy for unresectable stage III non-small-cell lung cancer patients treated with concurrent chemoradiation: a randomised phase II trial GFPC – IFCT 02-01☆

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KEYWORDS
Lung cancer;
Radiotherapy;
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Abstract ***Purpose:*** The objective of this randomised phase II study was to evaluate the impact in terms of response and toxicities of induction or consolidation chemotherapy respectively before or after concurrent chemoradiotherapy in unresectable stage III non-small-cell lung cancer.
Patients and methods: In the induction arm, patients received induction chemotherapy with cisplatin (80 mg/m^2) and paclitaxel (200 mg/m^2) on days 1 and 29 followed by a concurrent chemoradiotherapy (66 Gy in 33 fractions, cisplatin 80 mg/m^2 days 1, 29 and 57, vinorelbine 15 mg/m^2 days 1, 8, 29, 36, 57 and 64). In consolidation arm, the same concurrent chemoradiotherapy began on day 1 followed by two cycles of cisplatin and paclitaxel.
Results: One hundred twenty seven patients were randomised. The intent to treat response rates in induction and consolidation arms were 58% and 56% respectively. Median survival was 19.6 months in induction arm and 16.3 months in consolidation arm and 4-year survival rates were 21% and 30% respectively. Haematologic and non-haematologic toxicities were similar in both arms, except grade 3/4 oesophagitis, more frequent in consolidation arm than in induction arm (17% versus 10%).
Conclusion: Cisplatin-based chemotherapy as induction or consolidation with concurrent chemoradiotherapy can be administrated safely. Response rates were similar in both arms with a trend in favour for consolidation arm for long-term survival.

1. Introduction

About 30% of patients with non-small-cell lung cancer (NSCLC) have unresectable stage III disease at diagnosis. The current standard of care of these patients is concurrent treatment with platinum-based chemotherapy and thoracic radiotherapy [1–3]. Randomised clinical trials and meta-analyses have generally shown trends in favour of combination chemoradiotherapy compared with radiotherapy alone, as well as concomitant compared with sequential chemoradiotherapy [4–8]. While the data available provide general support for concurrent chemoradiotherapy, many important questions remain [9]. The combination of agents, the total dose delivered and the schedule of administration must all be considered in order to optimise the management of these patients and there are currently insufficient data in these areas [9].

The combination of third generation cytotoxic drugs and thoracic radiotherapy often needs a dose-reduction of chemotherapy due to increase of radiation therapy toxicity. Full dose chemotherapy before (induction chemotherapy) or after (consolidation chemotherapy) the concurrent chemoradiotherapy may help to eradicate the metastatic component of disease. The optimal sequencing between chemoradiotherapy and chemotherapy is still not well defined [8,9].

We decided to explore both induction and consolidation strategies in a randomised phase II setting. The objective was to evaluate the impact in terms of response and toxicities of both strategies using cisplatin-paclitaxel as induction or consolidation chemotherapy and cisplatin-vinorelbine during radiotherapy. We chose cisplatin-vinorelbine doublet for its good efficacy/toxicity profile when associated to thoracic radiotherapy [10–13]; cisplatin-paclitaxel doublet, tested in a large randomised phase III trial in stage IV NSCLC, showed a good response rate (28%) and a better overall survival (OS) compared to carboplatin/paclitaxel ($p = .019$) [14] and can be so considered as a good induction or consolidation chemotherapy. On the other hand, the use of docetaxel was proposed in this setting [15,16] but at the time of our study design, docetaxel was not approved in first line chemotherapy for advanced NSCLC by French health regulatory authorities.

2. Patients and methods

2.1. Eligibility criteria

The main inclusion criteria were: histogical proven NSCLC, unresectable stage IIIAN2 or stage IIIB without pleural involvement or supra-clavicular lymph nodes invasion, at least one measurable target, Eastern Cooperative Oncology Group score 0 or 1, weight loss less than 10%, age between 18 and 70 years, normal hepatic, renal and haematologic functions, with haemoglobin ≥9.5 g/dl, satisfactory respiratory function ($FEV_1 > 40\%$ of theoretical value and $PaO_2 > 60$ mmHg) and written informed consent. The main exclusion criteria were active uncontrolled infection, unstable cardio-vascular disease, peripheral neuropathy grade 1 or more, psychiatric or neurologic disorders, previous malignancy (except for in situ carcinoma of the cervix, basocellular skin cancer). Pre treatment assessment included laboratory test parameters, chest X-ray, bronchoscopy, chest and brain computed tomography (CT) scan, abdominal CT scan,

bone scan, and pulmonary function testing. Mediastinoscopy was not mandatory. Positron-emission tomography-scan was not systematically performed. Complete blood counts were done every week throughout the study. Every cycle of chemotherapy and every week during concurrent chemoradiotherapy, patients underwent a clinical examination focussing on cancer-related symptoms and treatment toxicities.

2.2. Treatment schedule

Patients were randomly assigned to receive induction or consolidation chemotherapy. In the induction arm, patients received two cycles of chemotherapy consisting of cisplatin 80 mg/m^2 and paclitaxel 200 mg/m^2 on days 1 and 22, followed by a concurrent chemoradiotherapy including thoracic radiation therapy and three cycles of cisplatin 80 mg/m^2 on day 1 and vinorelbine 15 mg/m^2 on days 1 and 8, repeated every 3 weeks. In the consolidation arm, the same concurrent chemoradiotherapy began on day 1 followed by two cycles of cisplatin and paclitaxel. Doses were adjusted according to blood cell counts, neurologic toxicity and renal function. In induction arm, for patients with no progression disease after induction, chemoradiotherapy began 4 weeks after the second cisplatin administration.

Radiotherapy was given to the primary tumour and involved lymph nodes at 2 Gy daily, 5 days per week over a period of 6.5 weeks. The total dose consisted of 66 Gy in 33 fractions. Radiotherapy was delivered with photon beams generated by a linear accelerator with an energy exceeding 6 MV and required personalised patient immobilisation and conformal 3D treatment planning. A minimum of six radiation fields was recommended. The planning target volume was the gross tumour volume (GTV) plus 1.5 cm margin without prophylactic nodal irradiation. In case of tumour response to the induction chemotherapy, GTV should encompass the pre-chemotherapy tumour volume, The maximum dose to any point in the spinal cord could not exceed 46 Gy. Dose-volume histograms were used to prevent pulmonary toxicity. V_{20} (total pulmonary volume receiving 20 Gy) and V_{30} (total pulmonary volume receiving 30 Gy) could be respectively inferior or equal to 30% and 20% of total pulmonary volume. If radiotherapy had to be interrupted more than 14 days because of toxicity, the patient was withdrawn from the study, but was included in the survival analysis. In both arms, medical treatment for oesophagitis started at grade 1. For each case, a central review of radiation therapy parameters (dose, radiation fields and dose-volume histograms) was performed by a panel of radiotherapists.

2.3. Study design and statistical analysis

Registration and randomisation were centrally performed. The primary end-point was the intent to treat objective response rate assessed by Response Evaluation Criteria in Solid Tumour (RECIST) criteria. Secondary end-points were (OS), progression-free survival (PFS) and toxicities. The trial was driven according the optimal two-stage design described by Simon [17]. Response was assessed at the end of the whole treatment. A response rate inferior or equal to 40% was considered as null hypothesis and without interest. Treatment was considered as clinically interesting if response rate was superior or equal to 60%. With an alpha risk of 0.05 and a beta risk of 0.10 in a one-sided test, the required sample size was 66 patients per arm. Interim analysis was performed after 25 inclusions in each arm. OS, updated in 2010, January, 1st, was calculated using Kaplan-Meier method from date of randomisation to death or last follow-up evaluation; PFS was defined as the time from randomisation until first event (local or distant progression or death).

Acute toxicities were graded according to standard National Cancer Institute-Common Toxicity Criteria criteria v 2.0 and Radiation Therapy Oncology Group tables [18]. Late radiotherapy toxicities were graded by SOMA-Late Effects of Normal Tissues (LENT) tables [19]. Responses were assessed by RECIST criteria [20]. In both arms, at the end of the whole treatment with a final evaluation was performed 8 weeks after the last administration of chemotherapy. An independent panel reviewed the imaging studies for staging and response evaluation. The data processing was performed using statistical analysis software packages version 9.2. A general descriptive analysis was done for every parameters of the study. The distribution of qualitative variables between groups was compared using chi^2 test. When the calculated frequency of the categorical data of the contingency table did not allow the use of the chi^2 test, Fisher's exact test was performed. Quantitative variables were compared using Wilcoxon test. A p level $< .05$ was considered as significant. The protocol was accepted by the ethical committee of Saint-Etienne and was in accordance with the ethical standards of Helsinki Declaration.

3. Results

3.1. Characteristics of the patients

One hundred thirty two patients were enrolled in 35 participating institutions. Nine centres enrolled more than 50% of the patients. Five patients were not eligible (one stage IV, one stage II disease, one with supraclavicular lymph node, one with small-cell lung cancer histology and the last with a too large tumour volume for thoracic radiotherapy as defined in the protocol). Thus 127 patients were assessable; (four were lost of follow-up when the database was closed on January 2010). Characteristics and prognostic factors were well

Table 1
Patient characteristics.

Characteristics	Induction arm n = 64 (%)	Consolidation arm n = 63 (%)
Age, years: median (range)	56.5 (40–69)	58.7 (42–70)
Sex: male	58 (91)	55 (87)
PS: 0/1	42 (66)/22 (34)	47 (75)/16 (25)
Histology		
Squamous cell	28 (44)	36 (57)
Adenocarcinoma	19 (30)	22 (35)
Undifferentiated	17 (26)	5 (8)
Stage of disease		
IIIAN2	13 (20)	17 (27)
IIIB	51 (80)	46 (73)

Table 2
Chemotherapy administration.

	Induction arm n = 64 (%)	Consolidation arm n = 63 (%)
Induction chemotherapy cycles		
1	2 (3)	–
2	62 (97)	–
Concurrent chemotherapy cycles		
0	13 (20)	2 (3)
1	2 (3)	1 (1.5)
2	7 (11)	5 (8)
3	42 (66)	55 (87.5)
Consolidation chemotherapy cycles		
0	–	10 (16)
1	–	8 (13)
2	–	45 (71)

balanced between the two arms except for histology with more squamous cell carcinomas and less undifferentiated carcinomas in the consolidation arm (Table 1).

3.2. Treatment administration

Overall, in induction and consolidation arms, 66% and 71% of patients respectively received the planned therapy and 66% and 87% the planned radiotherapy, p = 0.2 (Fig. 1). In induction arm, 2 patients did not receive the two cycles of induction chemotherapy (one for diseases progression and the other for severe infection) and 13 (20%) did not receive chemoradiation (five for disease progression, six for treatment-related toxicities and two for surgery after induction chemotherapy) (Table 2). In consolidation arm, 2 patients did not receive any chemoradiation (one for disease progression, the other for severe infection, arising between randomisation and the start of treatment) and 10 (16%) did not receive consolidation chemotherapy (one disease progression, four for treatment-related toxicities, three for severe infection, one for myocardial infarction and one patient refused).

3.3. Tolerance

Haematologic toxicities were similar in both arms (Table 3); grade 1/2 peripheral neuropathy was more frequent in consolidation arm than in induction arm (31% versus 21%). Renal toxicity was mild in both arms. Grade 3/4 oesophagitis occurred in 12% of patients in induction arm and in 17% of patients in consolidation arm. Grade 1/2 radiation pneumonitis was equally frequent in both arms (24% versus 25%). Treatment had to be stopped for toxicity in respectively 11 and 8

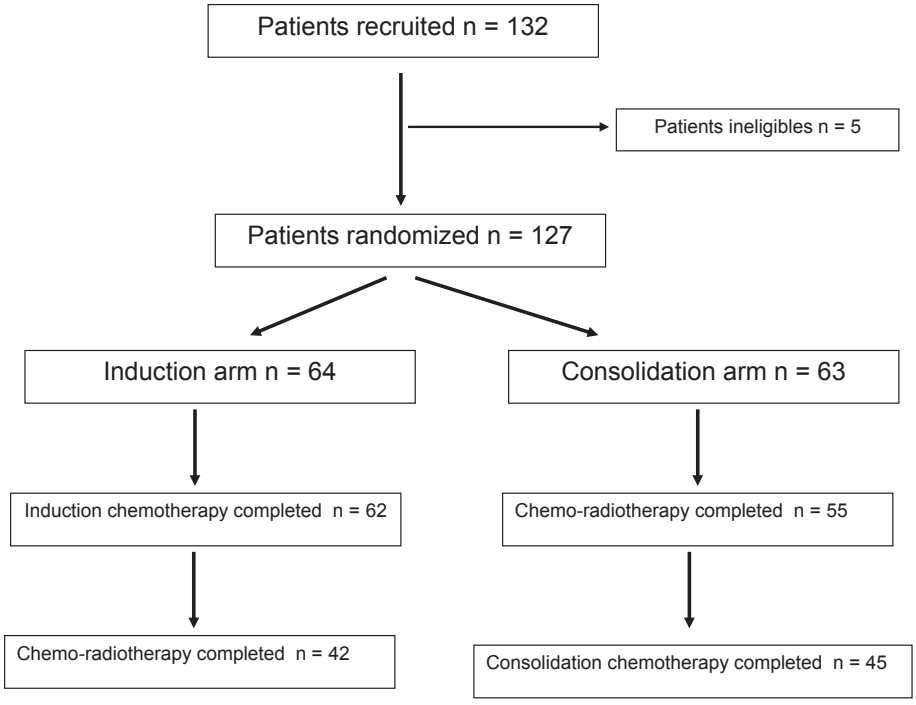

Fig. 1. Flow chart of the trial.

Table 3
Grades 3/4 adverse events (National Cancer Institute – Common Toxicity Criteria v 2.0) by treatment arm.

	Induction arm n = 64 (%)	Consolidation arm n = 63 (%)
Haematologic toxicities		
Neutropenia	27 (42.1)	32 (50.8)
Anaemia	4 (6.3)	9 (14.3)
Thrombocytopenia	1 (1.6)	4 (6.4)
Infection	3 (4.7)[a]	8 (12.8)[a]
Non-haematologic toxicities		
Renal	1 (1.6)	1 (1.6)
Neuropathy	1 (1.6)	–
Oesophagitis	6 (12)[b]	10 (17)
Pneumonitis	–	1 (1.6)[c]
Massive haemoptysia	1 (1.6)††	–

[a] One grade 5 severe infection in each arm during computed tomography/TRT.
[b] One grade 5 oesophageal toxicity (fistula).
[c] One grade 5 radiation pneumonitis 4 months after radiotherapy completion and one massive pulmonary haemorrhage.

patients in induction and consolidation arms. Five treatment-related deaths were observed (Table 3).

3.4. Outcomes

In induction and consolidation arms, 84% and 80% were assessable respectively with in intent to treat analysis, response rates of 58% and 56% respectively (Table 4). At the end of treatment, 19% and 21% in induction and consolidation arms experienced disease progression respectively.

Median survival, analysed after a median follow-up of 6.4 years, was 19.6 and 16.3 months in induction and consolidation arms respectively but the 4-year survival rates was 21% in the induction arm and 30% in the consolidation arm, p = 0.2 (Fig. 2). Median PFS was 9.7 months (95% confidence interval [CI], 8.5 to 12.3) in induction arm and 8.2 months (95% CI, 6.5 to 12) in consolidation arm (Fig. 3). Isolated loco-regional relapses were more frequent in induction arm than in consolidation arm (23% versus 13%), while the number of distant relapses was similar in both arms (29%).

Table 4
Outcomes (PFS: progression-free survival).

	Induction arm n = 64	Consolidation arm n = 63
Responses	54 (84%)	50 (80%)
Complete response	2 (3.2%)	3 (4.8%)
Partial response	35 (54.7%)	32 (50.8%)
Stable	5 (9.3%)	2 (3.2%)
Progressive	12 (18.6%)*	13 (20.6%)
Survival		
Median (months, 95% CI)	19.6 (17.2–25.6)	16.3 (10.2–27.8)
1-year	70% (59.1% –81.5%)	59% (46.5% –70.9%)
2-year	42% (30%–54.3%)	40% (27.6% –51.7%)
4-year	21% (11.1% –31.4%)	30% (18.6% –41.3%)
Median PFS (months, 95% CI)	9.7 (8.5–12.3)	8.2 (6.5–12)

CI = confidence interval.

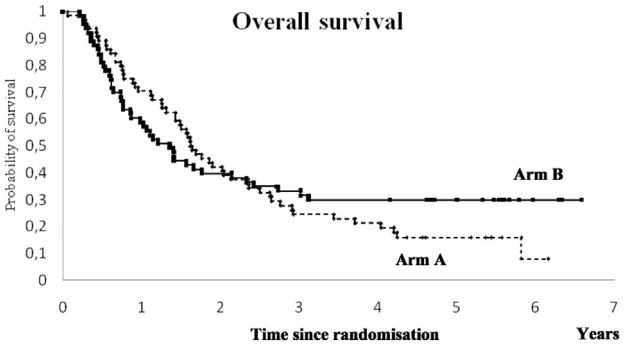

Fig. 2. Overall survival according to the treatment in the GFPC – IFCT 02-01 study. Arm A: induction arm and Arm B: consolidation arm (19.6 versus 16.3 months, p = 0.2). GFPC = Groupe Français de Pneumo-Cancérologie; IFCT = Intergroupe Francophone de Cancérologie Thoracique.

4. Discussion

With an intention to treat response rate of respectively 58% and 56% in induction and consolidation arms, this study did not reach its primary objective (response rate superior or equal to 60%). Nevertheless, this aim is obtained on assessable patients in both arms. In terms of survival, even if there was a trend toward a median survival benefit for induction arm, the 4-year survival rate appears better in consolidation arm than in induction arm (30% versus 21%). This survival advantage might be due to a higher proportion of patients receiving concurrent chemoradiotherapy in the consolidation arm. In induction chemotherapy only 66 % of patients

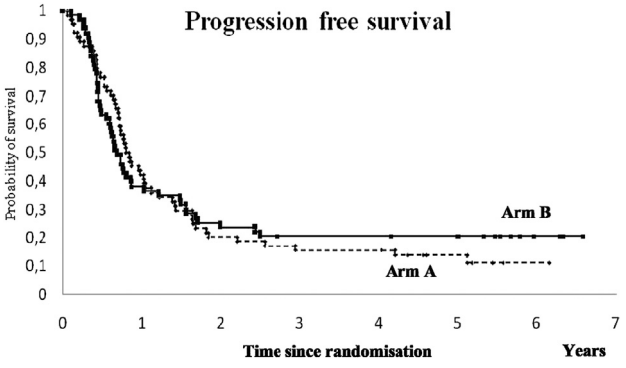

Fig. 3. Progression-free survival according to the treatment in the in the GFPC – IFCT 02-01 study. Arm A: induction arm, Arm B: consolidation arm (9.7 versus 8.2 months, p = 0.3). GFPC = Groupe Français de Pneumo-Cancérologie; IFCT - = Intergroupe Francophone de Cancérologie Thoracique.

received the planned radiotherapy, mainly because tumour progression or toxicity. Given that radiation therapy is a major component of locally advanced NSCLC management, induction chemotherapy may not be an optimal strategy in this setting.

Several randomised studies addressing the question of the optimal timing of chemoradiotherapy administration [3,21–24]. In a phase II non comparative randomised trial conducted to determine the optimal sequencing and integration of paclitaxel/carboplatin with standard thoracic radiotherapy in patients with locally advanced unresected stage III NSCLC [3] 257 patients were randomised between 1) sequential induction chemotherapy and radiotherapy, 2) induction chemotherapy followed by concurrent chemoradiotherapy and 3) concurrent chemoradiotherapy followed by consolidation chemotherapy. Median survival was slightly increased with consolidation chemotherapy (16.3 months) than with the sequential (13 months) or induction chemotherapy (12.7 months) arms; in induction and consolidation arms, respectively 69% and 74% patients received the planned therapy. In our study, we observed very close results with 66% and 71% of patients received the planned therapy in induction and consolidation arms respectively. A Belgian study [21], designed as a phase III randomised trial comparing induction chemotherapy followed by concurrent chemoradiotherapy and concurrent chemoradiotherapy followed by consolidation chemotherapy was inconclusive, prematurely stopped for poor accrual. In a Spanish phase 2 study [22] induction and consolidation chemotherapies consisted in a non-platin based regimen (docetaxel and gemcitabine) and chemoradiotherapy associated docetaxel 20 mg/m^2 and carboplatin Aire under the curve 2 weekly plus 60 Gy; no differences were found between the two arms with a responses rates of 56% and 57% and a median survival of 13.07 and 13.8 months respectively. The use of non-platin chemotherapy could explain the lower results. Finally, studies using cisplatin-docetaxel as induction or consolidation doublet and also in association with thoracic radiotherapy also failed to show a superiority of one sequence over other [23,24]. However in this setting of locally advanced NSCLC, as recently published [9,25], chemoradiotherapy can be considered the standard.

In our study, treatment-related toxicities rates were similar to those observed in others studies with concurrent chemoradiotherapy. Oesophageal and pulmonary toxicities were lower than in Cancer and Leukemia Group B 9431 trial [26], whereas total dose of radiotherapy was identical. These lower incidences could be explained by the use of conformal 3D radiotherapy and V_{20} less than 30% to prevent pulmonary toxicity. The incidence of toxic deaths (4%) was lower than in our previous study (9.5%) and congruent with other trials [7,27,28]. This is probably due to a better selection of patients and the use of a less toxic chemotherapy regimen for induction or consolidation.

In conclusion, our study demonstrated the feasibility of cisplatin-based chemotherapy as induction or consolidation with concurrent chemoradiotherapy but as observed in other randomised trials, failed to demonstrated consistent benefits of one of the strategy over the other. Progress may be obtained by a better staging and selection of patients, an improvement of radiotherapy techniques and association combining new agents with chemoradiotherapy.

Conflict of interest statement

All the authors declare no conflict of interest in relation with this work.

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