Cisplatin-Based Three Drugs Combination (NIP) as Induction and Adjuvant Treatment in Locally Advanced Non-small Cell Lung Cancer

Final Results

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Introduction: This phase III trial was conducted in non-small cell lung cancer patients with locally advanced stage II B (only T3N0) III A and III B (only T4 N0). Primary endpoint was 2-year survival; secondary were toxicity, disease-free survival, and overall survival.
Methods: After three cycles of vinorelbine (N) 25 mg/m^2 on days 1 and 5, ifosfamide/mesna (I) 3 g/m^2 on day 1, cisplatin (P) (NIP), patients were treated by surgery and within 45 days were randomized to two additional cycles of NIP versus observation.
Results: Median tumor diameter was 5.5 cm (1.2–10.6). Overall, 155 of 156 patients received chemotherapy: 133 (85%) men, median age: 59 years (35–75). Sixty-five percentage of patients were stage III A, 28% II B, and 7% III B. The study has been closed prematurely because of the low inclusion rate. After three cycles of induction in 143 assessable patients, 82 reported an objective response (57.3%) (95% CI: 48.8–65.6), with 3.5% complete response and 53.8% partial response. Relative dose intensity during neoadjuvant NIP (%) was 97, 98, and 98.5 for vinorelbine, ifosfamide/mesna, and cisplatin, respectively. Tolerance: G3 to 4 neutropenia in 3% of patients and G3 to 4 anemia in 4%; nonhematological toxicities included G3 nausea/vomiting in 11%, G3 anorexia and G3 to 4 infection in 6.5%, G3 asthenia in 10% and G3 to 4 alopecia in 25.5%. After a median of 32 days after NIP, 107 patients (69%) underwent operation with complete resection (R0) in 74% (79 of 107 patients). Downstaging (N2 to N0) after surgery was 29%. Operative mortality rate was 2.8%. Twenty-one days (median) after surgery, 79 patients were randomized to adjuvant NIP (47%) or control (53%). Tolerance of adjuvant NIP: 12.5% G3 to 4 nausea/vomiting, 19% G3 alopecia, 6% G3 infection, and G3 asthenia. Overall median survival 32.3 versus 31.8 months in the observation and NIP arms, respectively.
Conclusions: NIP allows 74% of R0 with no surgery delay. The few number of randomized patients did not allow to conclude on the efficacy of adjuvant chemotherapy.

Key Words: Triplet combination, Downstaging, Stage III, Non-small cell lung cancer, Neo-adjuvant chemotherapy, Adjuvant chemotherapy.

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Stage III non-small cell lung cancer (NSCLC) is a combination of different conditions with different strategies of treatment. Even if completely resected, patients with ipsilateral mediastinal lymph nodes (N2) involvement will develop distant metastasis.[1]

In fact, complete resection for patients with stage IIIa is feasible in selected cases but the 5 years' survival of patients presenting clinical evidence of N2 disease remains poor, about 8%, even in patients completely resected.[2]

The role of induction chemotherapy (CT) in the treatment of stage III patients remains uncertain. Several phase II showed encouraging results reducing the tumor bulk in 50 to 70% of patients. Two small phase III trials performed at the same time in Europe and North America[3] demonstrated significant benefit in terms of median survival versus surgery alone. Unfortunately, Depierre et al.[4] showed, in a large phase III trial, a significant reduction in development of

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distant metastasis in patients who received CT but with no impact on the overall survival.

The combination of vinorelbine/ifosfamide/cisplatin (NIP) reported high activity in several phases II and III studies in terms of response rate and 1 to 2 years' survival in patients with stages IIIB and IV disease.[5–7] Based on these data, a phase II trial using this combination of three drugs in locally advanced NSCLC reported an interesting 61% response rate with 21.4 months of median survival.[8]

When the present study was set up, a meta-analysis on adjuvant chemotherapy reported that the administration of CT after complete surgical resection may reduce local treatment failures by eradicating circulating tumor cells and subclinical metastasis still present at the time of surgery.[9] The objective of the current study was to test the activity of a new schedule of intravenous vinorelbine (on days 1 and 5) in combination with ifosfamide/mesna and cisplatin (on day 1) every 21 days as primary chemotherapy in patients with previously untreated stage III A/B NSCLC, to determine both the tolerance and the efficacy of this combination in terms of response rate (clinical and pathologic), lymph node downstaging (N2 to N0), and overall survival.

The protocol followed the recommendations of the Helsinki Declaration and was approved by the Ethics Committee of the participating institutions.

PATIENTS AND METHODS

Main Inclusion and Exclusion Criteria

Patients to be included in this trial had to present histologic and/or cytologic evidence of NSCLC, locally advanced disease (T3/T4 N0 or IIIa tumors), without any previous treatment, aged more than 18, with Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 and life expectancy ≥ 3 months, at least one assessable lesion, with blood and biochemical parameters within the normal ranges for each institution and had to have signed the informed consent. Additional clinical features which precluded entry to the trial were superior vena cava syndrome, central nervous system metastasis, and second malignancy (except adequately treated basal cell carcinoma of the skin and carcinoma in situ of the uterine cervix). Active infectious disease, pregnancy, neurologic disorders which could interfere with the evaluation of neurologic toxicity and mentally incapacitated patients, family, social or environmental conditions impairing adequate follow-up and protocol compliance were also excluded.

Patients participating in other investigational drug trials during the previous 30 days, or pregnant or breast-feeding were not eligible to participate in the study.

Pretreatment evaluation was completed within 2 weeks before entry on study including clinical examination, chest radiographs, chest computed tomography scan, abdominal/pelvic ultrasound or computed tomography scan, bronchoscopy, fine-needle aspiration or mediatinoscopy (only if the patient presented with N^+), brain computed tomography scan, and bone scan (only if clinical indicated). Efficacy and tolerance were evaluated according to the World Health Organization (WHO) criteria.

Treatment Plan

The NIP chemotherapy was administered as follows: vinorelbine (N) 25 mg/m^2 IV on days 1 and 5, ifosfamide/mesna (I) 3 g/m^2 on day 1, cisplatin (P) 80 mg/m^2 IV on day 1 repeated every 21 days. Three courses of NIP were given unless rapid disease progression occurred.

Chemotherapy doses were not escalated in this protocol. All three drugs could be reduced depending on the WHO grade (3–4) of toxicity from 50 to 100%. Dose reduction was allowed based on hematological, neurologic, hepatic, or renal toxicity. Low blood counts at day 21 led to treatment delays of 1 or 2 weeks until blood recovery (whole blood cell $\geq 3000/mm^3$, absolute neutrophil count $\geq 1500/mm^3$, platelets $\geq 100{,}000/mm^3$). A maximum delay of 3 weeks was allowed, beyond which the treatment was discontinued and the patient withdrew from the study. For other grade 3 to 4 toxicity, the same rules were applied. Monitoring of the full blood count before day 21 was not made systematically and nadir counts were therefore not documented. Preventive colony-stimulating factors were not allowed except in case of febrile neutropenia and dose reduction was required for the subsequent cycle.

Grade 3 to 4 neurologic toxicity (including paresthesia, muscle weakness, or paralytic ileus) resulted in treatment discontinuation.

Chemotherapy Administration

Vinorelbine (Navelbine) was administered in a 6- to 10-minute infusion followed by a free running 500 ml normal saline solution for rinsing the vein; ifosfamide was diluted in 500 ml of normal saline solution with mesna 3 g/m^2 on day 1 and infused more than 3 hours. Cisplatin was diluted in 250 ml of normal saline solution and administered more than 1 hour and within 1 hour after the end of infusion of vinorelbine. Cisplatin hydration and antiemetic therapy would be given according to the center clinical practice. All three drugs were administered every 21 days. Before receiving each cycle, patients had to have a complete blood count and biochemical evaluation. Moreover, a blood count had to be repeated before vinorelbine administration on day 5.

Surgery

After the third course, a full assessment was performed. Operable patients with complete response, partial response, or stable disease underwent operation. If no response could be observed, patients were withdrawn from the study.

Adjuvant Chemotherapy and Follow-Up

After operation, only patients with complete resection (R0) were randomized; patients partially resected or not resected were withdrawn from the study.

Thus, patients were randomly allocated to either two further cycles of chemotherapy with the same schedule as during neoadjuvant (arm A) or to observation without any treatment (arm B). Radiotherapy was not allowed in either group. Patient removed from study had to be evaluated for the calculation of survival rates. All patients were routinely followed by physical examination, complete blood count,

chemistry, thoracic computed tomography scan, and upper abdominal computed tomography scan.

Statistical Considerations

For the patients subjected to induction treatment, followed by surgery alone the expected 2-year survival was 25%. For a suitable additional benefit from postoperative NIP an absolute improvement in the 2-year survival with at least 45% of patients alive at 2 years was planned.

To have 90% confidence, with a two-sided 5% level test, for detecting the above difference in survival, 62 patients were needed to be randomized. Taking into account that 20 to 30% of included patients would fail the induction treatment 150 patients were needed to be included. The number of patients lost to follow-up was evaluated at 10% of the total number of subjects. Therefore, the total sample size for the study was of 150 eligible patients with 62 patients included in each treatment group.

Secondary endpoints included disease-free survival and safety. Time-dependent parameters were described using Kaplan-Meier curves and life tables by treatment arm. Overall survival and disease-free survival were compared using a two-sided logrank test.

Overall survival was defined as the time elapsed from the date of registration on one hand and randomization on the other hand until death because of any cause or to last follow-up. Patients alive at the cutoff date or lost to follow-up were censored at the date of last news. Disease-free survival was defined as the time elapsed from the date of randomization until relapse or death because of any cause or last follow-up date. Patients without relapse at the cutoff date or lost to follow-up were censored at the date of last news.

Maximum WHO grade (or severity) was reported by cycle and by patient for hematological and nonhematological toxicities.

Continuous data were summarized with the following items: frequency, median, range, mean, and standard error if relevant. Categorical data were summarized in contingency tables with frequencies and percentages of each modality (including missing data modality).

All analyses were performed using SAS system software version 8.2 (SAS Institute, Inc., Cary, North Carolina) for Windows.

RESULTS

From January 1999 through October 2002, a total of 156 patients were included (Figure 1). The study has been closed prematurely because of the low rate of inclusions, with only the half of the planned patients randomized after 4-year inclusion period.

Of the 156 patients included in the protocol, 155 received the induction treatment. Only one patient died just before to be treated because of progression. Although this patient was excluded from the analysis, he was included in the patient characteristics (Table 1).

Median age was 59 years (range 35–75 years) and the most common histology was squamous cell (52% of the population). All but two patients presented a performance status 0 to 1. Clinical stage was determined according to the baseline computed tomography scan. All patients presenting N positive at the computed tomography scan received a mediastinoscopy for histologic confirmation. Most of the patients (65%) presented stage IIIa, 28% stage IIb, and 7% stage IIIb. At the beginning of the study, only stage IIIa was eligible for this protocol that included T3N0. After the changes of the classification and the introduction of T3N0 into stage IIb,[10] these patients continued to enter into the study, explaining why almost one third of patients had stage IIb.

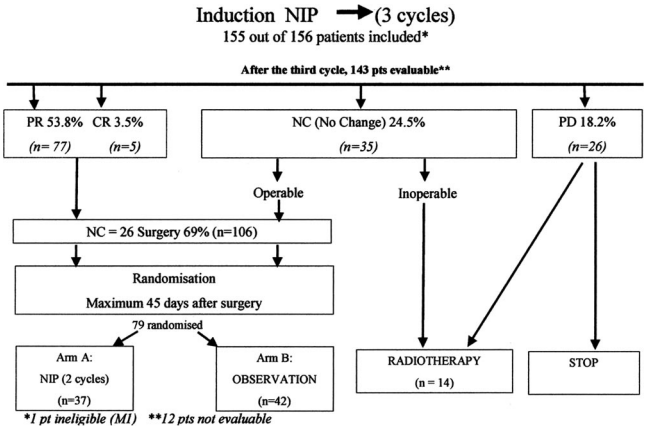

FIGURE 1. Study flow chart.

TABLE 1. Patients Characteristics (n = 156)

	No. of Pts	Percent
Median age, yr (range)	59 (35–75)	
Male	133	85
Female	23	15
Histology		
Squamous cell	82	52
Adenocarcinoma	48	31
Large cell carcinoma	9	6
NSCLC (NOS)	17	11
Stage at diagnosis		
IIB	43	28
IIIA	102	65
IIIB	11	7
Performance status		
0–1	154	99
2	2	1
Median T diameter, cm (range)	5.5 (1.2–10.6)	
N0	53	34
N1	2	1
N2	101	65

Induction CT

Patients received a total of 435 cycles of CT. The median number of cycles was 3 (range, 1–3) with 136 patients receiving the whole number of cycles as per protocol. The relative dose intensity for vinorelbine, ifosfamide, and cisplatin was 97, 98, and 98.5%, respectively.

TABLE 2. Response to Induction Chemotherapy

	ITT		Assessable	
	No. of Pts	Percent	No. of Pts	Percent
Clinical CR	5	3.2	5	3.5
Partial response	77	49.4	77	53.8
ORR (95% CI)	82	52.6 (44.4–60.6)	82	57.3 (48.8–65.6)
No change	35	22.4	35	24.5
Progressive disease	26	16.7	26	18.2
Not evaluable	13	8.3	—	—
Total	156	100	143	100

Response to induction CT

The results of the induction step are listed in the Table 2. Thirteen patients were considered as not assessable. The reasons are death (six patients), refusal (two patients), lost of follow-up (one patient), toxicity (one patient), acute pancreatitis (one patient), investigator decision (one patient), unknown (one patient). The six deaths occurred for toxicity in three patients (1.9%), sudden death in one (0.6%), heart attack in one (0.6%), and complication of malignant disease in one (0.6%).

The overall response rate was 52.6% in the intent-to-treat (ITT) population and 57.3% in the assessable population. Instead, 22.4% of ITT patients and 24.5% of assessable patients had stable disease, 16.7 and 18.2% progressed to the induction CT in the ITT and assessable patients, respectively.

Surgical Outcomes

Overall, 107 of 155 treated patients (69%) were eligible for operation (Table 3). The delay between the last NVB administration and operation was 32 days (range, 21–67 days).

Lobectomy was performed in 55 patients (52%); it was right in 35 patients (65%), left in 19 (35%), and for 1 patient the site was not specified. Pneumonectomy was performed in 42 patients (39%). It was right in 20 patients (49%) and left in 21 patients (51%) and for 1 patient the site was not specified. A right atypical segmentectomy was performed in only one patient (1%). Finally, in nine patients only an exploratory thoracotomy (8%) was performed.

A complete resection (R0) was possible in 79 of 107 patients (74%). In five patients, there was not tumor left (pathologic complete response, pCR) (5%) and downstaging from N2 to N0 was seen in 29% of the patients.

TABLE 3. Type of Surgery

	Right		Left	
	n	Percent	*n*	Percent
Lobectomy ($n = 55$)[a] (52%)	35	65	19	35
Pneumonectomy ($n = 42$)[a] (39%)	20	49	21	51
Explorative thoracotomy ($n = 9$) (8%)	3	33	6	67
Atypical segmentectomy ($n = 1$) (1%)	1	100	—	—
Total	59		46	

[a] For one patient each, the side is not specified.

Only three patients presented perioperative complications: intestinal obstruction (one patient), bronchial infection (one patient), and infection with empyema (one patient). Three patients died within 30 days after surgery: one patient for respiratory insufficiency, one for acute myocardium infarction, and one for pulmonary edema.

Adjuvant Treatment

All 79 patients with complete resection were randomized to either two more cycles of NIP chemotherapy (37 patients) or observation (42 patients).

Survival

After a median follow-up of 48 months from registration, the median survival was 31.8 months in the NIP arm and 32.3 months in the observation arm (Figure 2). Disease-free survival was identical in both arms, 16.8 months (Figure 3).

Overall survival at 1, 2, and 3 years was of 91.9, 62.2, and 48.7% in the treatment arm and of 85.7, 59.5, and 47.1% in the observation arm (Table 4).

If we consider median survival from randomization, there was neither difference in terms of median survival: 27.8 versus 28.7 months in the NIP and observation arms, respectively (Figure 4).

Tolerance

One hundred and fifty-three patients received at least one cycle of CT and were assessable for tolerance.

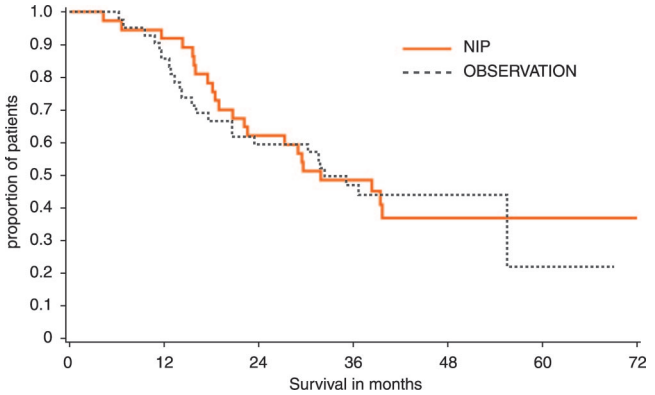

FIGURE 2. Overall survival from registration.

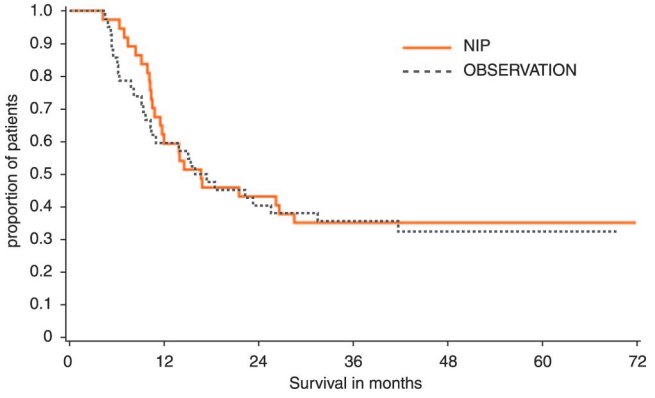

FIGURE 3. Disease-free survival from registration.

TABLE 4. Overall Survival from Registration

	NIP (n = 37)	Observation (n = 42)
Median survival (m)	31.8	32.3
Relapse-free survival (m)	16.8	16.8
1-yr survival (%)	91.9	85.7
2-yr survival (%)	62.2	59.5
3-yr survival (%)	48.7	47.1
Deaths	22 (59.5%)	24 (57.1%)

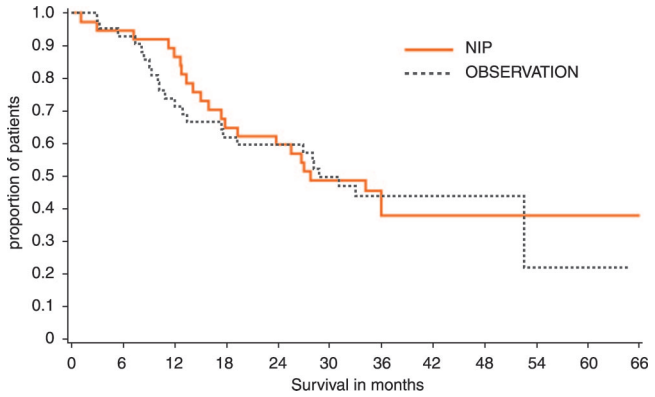

FIGURE 4. Overall survival from randomization.

TABLE 5. Main Haematological Adverse Events (per Assessable Patient for Toxicity) Grade 3–4 WHO Classification

	Neoadjuvant (n = 153)		Adjuvant (n = 29)		Control (n = 28)	
	n	Percent	n	Percent	n	Percent
Anemia	6	4	—	—	—	—
Neutropenia	5	3	—	—	—	—
Thrombocytopenia	—	—	—	—	—	—
Death	6[a]	4	1	3	—	—
	(n = 153)		(n = 32)		(n = 35)	
Nausea/vomiting	17	11	4	12.5	—	—
Diarrhea	5	3	—	—	—	—
Alopecia	39	25.5	6	19	—	—
Infection	10	6.5	2	6	1	3
Asthenia	15	10	2	6	1	3
Pain	8	5	—	—	2	6
Anorexia	10	6.5	—	—	1	3

[a] Only because of toxicity (2%).

Febrile neutropenia was reported in 31 patients (20%), and it was the cause of death of two patients. Grade 3 to 4 anemia was rare, only in six patients (4%) (Table 5).

Among grade 3 to 4 nonhematological toxicities during neoadjuvant treatment, the most frequent was alopecia in 25.5% of patients, followed by nausea/vomiting (11%), asthenia (10%), anorexia (6.5%), pain no otherwise specified (5%), and infection (6.5%). Other toxicities were rare and accounted for less than 5%.

DISCUSSION

The theoretical benefits in performing induction CT before surgery in locally advanced NSCLC mainly include the cytoreduction of the bulky disease (downstaging) and the early control of the micrometastasis.

During the last 10 years, several phase II studies have shown that induction CT allowed to perform complete resection with pCR evidenced in 5 to 15%, being predictive of long-term survival. A phase III study failed to show any difference in terms of survival for the neoadjuvant treatment. Moreover, patients with stages Ib and II had more advantages from neoadjuvant than patients with stage IIIa. Nevertheless, this data, although interesting, have to be interpreted with caution as the study was not stratified by stage.[4]

In the current study, 155 patients received CT as induction. The response rates of 57% in assessable patients are in line with the results obtained by other phase III trials as well the pCR of 5%.

Concerning the choice of a combination of three drugs instead of a doublet, at the time the protocol was written, there was no final conclusion about two or three drugs combination, whereas in metastatic disease doublets seem to do better than three drugs combinations.[7] Thus, this question remains still open for locally advanced disease. The number of cycles needs some considerations. At the time of the study implementation, there were no data available evaluating if four cycles were better than two cycles of adjuvant chemotherapy. Thus we decided to keep only two cycles considering that the previous two cycles given as neoadjuvant chemotherapy may impact on controlling the micrometastasis.

The NIP combination did not increase postoperative complications even in patients with pneumonectomy.

In a meta-analysis carried out by Andre et al.,[11] neoadjuvant chemotherapy did not increase perioperatory mortality. In our study, only six patients showed complication or death, which represented 6%, in line with the data presented by Andre et al.

Large phase III trials reported that adjuvant CT is useful in stages II and III NSCLC, but the current trial failed to show any advantage of such approach, because of the low number of randomized patients, as well probably to the use of a triple combination chemotherapy which so far has not reported improvement in survival.

In our experience, the NIP combination was well tolerated with acceptable hematological/ nonhematological toxicity. The febrile neutropenia rate of 20% was quite higher but seldom complicated.

The three drugs combination (NIP) demonstrated to be effective in patients with unresectable pN2/bulky T4 tumors with optimal tumor shrinkage: 74% complete resection (R0) and downstaging (N2 to N0) confirmed by surgery in 29% of the patients.

Surgery was performed on time, within a median delay of 32 days after the last administration of NIP. Complications/deaths were rare after operation.

New approaches should be investigated to allow higher pCR with eventually combining chemotherapy with other treatment as radiotherapy. Recent data confirms that improve-

ment in survival may be achieved by this combination in those patients with pCR. In absence of pCR no advantages seem to be reported by the addition of surgery.[12]

Additional research should be focused on treatment customization based on the biology of the tumor, according for example, either to the expression of BRCA1[13] or to the sensitivity to targeted agents.

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