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# Pilot Study of Neoadjuvant Ifosfamide, Cisplatin, and Etoposide in Locally Advanced Non-small Cell Lung Cancer

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**33 patients with locally advanced non-small cell lung cancer entered a study of neoadjuvant chemotherapy to evaluate the response rate with ifosfamide/cisplatin/etoposide and the complete resection rate and safety of surgery following chemotherapy. Chemotherapy with cisplatin 25 mg/m$^2$, ifosfamide 1.5 g/m$^2$, and etoposide 100 mg/m$^2$ was given on days 1–4 of a 21 day cycle and repeated for three cycles. For responders, surgery was done 15–20 days after haematological recovery. Chemotherapy induced 5 complete responses (15%) and 18 partial responses (55%). 77% of the 33 patients had grade 3–4 neutropenia and 60% grade 3–4 thrombocytopenia. 1 patient died with a central nervous system haemorrhage. Thoracotomy was done in 21 patients but resection was only possible in 20 (61%). A complete resection was achieved in 18 patients (55%). Histology was negative for the 5 complete responses. Surgery induced no morbidity. A high response rate may be obtained with ifosfamide, cisplatin and etoposide neoadjuvant chemotherapy allowing a high complete resection rate.**
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## INTRODUCTION

LOCALLY advanced non-small cell lung cancers (NSCLC) have a poor prognosis following surgery alone because of a high rate of local and metastatic relapses [1, 2]. 5 year survival for these patients ranges between 5 and 15% [2–5]. Thus, locally advanced NSCLC for which resection is potentially possible but poorly curative is usually designated as marginally resectable [6]. Adjuvant postoperative chemotherapy or radiation therapy hardly improves survival [7, 8]. Therefore, other combined treatments might be proposed.

Neoadjuvant chemotherapy may be used for NSCLC to improve the complete resection rate and to treat non-detectable metastatic disease [9]. Encouraging results have been obtained (see Refs 10–13 for examples). Overall response rates ranging between 50 and 87% are higher than those in primary chemotherapy trials in advanced and/or metastatic NSCLC. Moreover, complete resection can be achieved in more than half the patients receiving neoadjuvant chemotherapy. However, whether such chemotherapy can reverse unresectable NSCLC into a resectable condition cannot be answered because of heterogeneity of staging and resection procedure.

Ifosfamide is one of the most effective cytostatics in NSCLC [14–16]. Combination chemotherapy (cisplatin and vindesine, or cisplatin, doxorubicin, and cyclophosphamide) has given a survival benefit to patients with advanced NSCLC [17]. Cisplatin plus etoposide has also been widely used [18]. Since synergy may occur, cisplatin/etoposide/ifosfamide is a reasonable combination to test in marginally resectable NSCLC. We have done a multicentred phase II study of this combination as neoadjuvant chemotherapy in locally advanced NSCLC to assess the complete and partial response rate, the pathological complete resection rate obtained by surgery for responder patients and surgical morbidity.

## PATIENTS AND METHODS

### *Patients*

Patients of both sexes with locally advanced and histologically proven NSCLC were entered. Inclusion criteria were: age below 75, WHO performance status 2 or under, weight loss 10% or less, respiratory function compatible with surgical resection (by perfusion/ventilation scanning), normal baseline renal and cardiac functions, and baseline neutrophils 2000/μl or more and platelets 100,000/μl or more. No patient had received previous therapy or had simultaneous malignant disease.

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Study design was approved by the Ethics Committee of Montpellier University where the coordination centre was located. Verbal informed consent was obtained from each patient before treatment.

*Staging*

Staging was done by exhaustive procedure according to the 4th edition of the UICC TNM classification and the American Thoracic Society map of regional pulmonary nodes. In particular, we analysed the mediastinal lymph-node involvement (N2). For all patients staging included clinical examination, chest X-rays, computed tomographic scan of chest, upper abdomen and brain, fiberoptic bronchoscopy, liver sonography and bone scanning. Each case was discussed by a medical panel of thoracic surgeons, chest physicians, radiologists and medical oncologists. Patients with distant metastatis (M1) were not eligible. Patients with gross mediastinal involvement (i.e. more than two ipsilateral nodal stations with mediastinal lymph nodes greater than 20 mm on computed tomography [CT] and widened carina or main bronchus distortion suggestive of subcarinal lymph nodes, were considered as having locally advanced NSCLC and were included in the study. Patients for whom staging failed to demonstrate mediastinal involvement had additional invasive staging with cervical mediastinoscopy, pulmonary angiography or thoracotomy before being entered.

*Treatment*

Chemotherapy consisted of daily intravenous infusion of etoposide 100 mg/m$^2$ over 30 min, cisplatin 25 mg/m$^2$ over 2 h, ifosfamide 1.5 g/m$^2$ over 3 h and mesna 1.8 g/m$^2$ over 14 h. The patients received hyper-hydration and was repeated on days 1–4. The cycle was repeated every 21 days for three cycles if neutrophils were 1500/μl or higher, platelets were 100,000/μl or higher and creatinine clearance was 60 ml/min or greater. Toxicity was assessed with the WHO scale.

*Assessments and resection*

Patients were evaluated for response at the start of each cycle of chemotherapy by clinical examination and chest X-ray. Based on the response after the second cycle of chemotherapy, patients with evidence of reponse were staged again and a resection was planned at that time. Other patients underwent a third cycle before staging again. Response to chemotherapy was evaluated with CT of the chest. A complete clinical response (CR) was defined as complete disappearance of all tumour lesions with a negative histological examination of a bronchial biospy specimen. A partial response (PR) was defined as a 50% or more reduction in the product of the two longest perpendicular diameters of the indicator lesions. Stable disease (SD) was defined as a less than 50% reduction or a less than 25% increase in this product indicator lesion. Progressive disease (PD) was defined as a 25% or greater increase in this product of the indicator lesions or appearance of new lesions.

For patients who achieved CR or PR a thoracotomy was scheduled 2 weeks after haematological recovery with an attempt at curative resecton and mediastinal lymph-node dissection. A complete resection was defined as resection of all macroscopic disease and normal histology of the margin. Other resections were considered as incomplete. Post-operative radiation therapy was delivered to the mediastinum (45 Gy) and the supraclavicular region (45 Gy). Patients with histologically proven nodal involvement at time of surgery received three additional cycles of chemotherapy.

Patients with SD or PD were not planned for surgery; radiation therapy was delivered to the primary tumour and mediastinum. Afterwards the best supportive care was given to these patients.

After completion of treatment all patients were followed up every 3 months. Survival was defined as the time from the first day of treatment to death.

## RESULTS

*Patients' characteristics*

Between September 1987 and September 1989, 33 patients from four institutions were enrolled (Table 1). All patients had measurable, pathologically confirmed NSCLC.

For all patients, staging disclosed gross mediastinal lymph-node involvement (N2) with at least two ipsilateral nodal stations involved, inducing main bronchus distortions. Invasive staging techniques were needed in 10 of the 33 patients: 1 patient with a squamous cell carcinoma of the left upper lobe had a pulmonary artery involvement demonstrated by angiography; 7 patients (2 adenocarcinomas, 5 squamous cell carcinomas) underwent a cervical mediastinoscopy which demonstrated pathologically confirmed metastases of paratracheal and/or pretracheal lymph nodes; and 2 patients (1 large cell carcinoma of the right upper lobe and 1 adenocarcinoma of the left upper lobe) underwent prestudy thoracotomy which demonstrated unresectable tumour with mediastinal invasion. According to the new international staging system [19], 32 patients were stage IIIa and 1 was stage IIIb.

*Response*

25 patients received three cycles of chemotherapy whereas 4 patients received only two cycles because of response after the second cycle. 1 patient died after the first cycle and 2 patients refused to continue the treatment after the first cycle because of major digestive toxicity. Treatment was discontinued after the

*Table* 1. *Patients' characteristics*

| | |
|---|---|
| No. | 33 |
| M/F | 31/2 |
| Mean age (S.D. range) | 56 (10, 42–74) |
| Histology | |
| Squamous cell carcinomas | 22 |
| Adenocarcinomas | 5 |
| Large cell carcinomas | 6 |
| Performance status | |
| 0 | 4 (12%) |
| 1 | 19 (58%) |
| 2 | 10 (30%) |
| Mediastinal extent by: | |
| CT | 23 |
| Biopsy | 9 |
| Pulmonary angiography | 1 |
| Prestudy staging | |
| IIIa T3N2M0 | 30 |
| T2N3M0 | 2 |
| IIIb T4N2M0 | 1 |

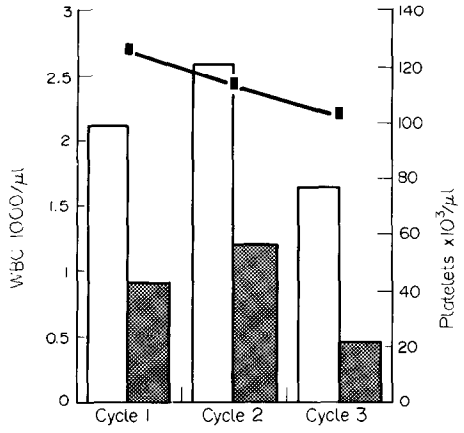


**Fig. 1. Haematological toxicity of ifosfamide/cisplatin/etoposide preoperative chemotherapy. Nadirs of leucocyte (WBC, open columns), neutrophil (closed columns) and mean platelet counts (line).**

second cycle in 1 patient who had deterioration in performance status. These 4 patients were classified as non-responders.

Objective responses were obtained in 23 patients (70%). Among these 5 (15%) achieved CR and 18 (55%) PR. 3 patients had SD, 7 (20%) progressed: central nervous system metastases in 3, adrenal gland metastases in 1, pulmonary lymphangitis in 1 and local progression in 2.

*Toxicity*

Haematological toxicity was moderate to severe but manageable. Nadirs were completely evaluated in 29 patients (88%). Mean nadir white cell and neutrophil counts ($\times 10^3/\mu l$) were respectively 2.13 and 0.91 for the first cycle, 2.6 and 1.21 for the second cycle and 1.66 and 0.46 for the third cycle. Mean nadir platelet counts (/μl) were 125,000 for the first cycle, 113,000 for the second cycle and 102,000 for the third cycle (Fig. 1). Grade 3–4 leucopenia occurred in 77% of the patients and grade 3–4 neutropenia in 94% (Table 2). The frequency of grade 3–4 haematological toxicity increased from cycle one to three and led to dose reduction in 4 patients. Among the patients with neutropenia, 10 had a grade 2–3 infection requiring antibiotics. Blood transfusions were given to 6 patients because of grade 3–4 anaemia. One fatal reaction was due to central nervous system haemorrhage induced by grade 4 thrombocytopenia. Nausea and vomiting occurred in 93% of the patients and required rehydration in 3 patients. We observed no ifosfamide-induced haematuria or encephalitis.

*Surgery*

Thoracotomy was done in 21 patients (5/5 CR and 16/18 PR, Fig. 2). For these patients, time between the start of chemotherapy and surgery ranged from 8.5 to 15 weeks (mean 11). No surgery was planned for 2 PR patients for whom gross mediastinal involvement remained despite objective response of the primary tumour. Of the 21 patients who underwent thoracotomy, a resection was possible in 20 (61% of evaluable patients; 14 pneumonectomies, 6 lobectomies). A complete resection was achieved in 18 patients (55% of evaluable patients and 82% of thoracotomies) without technical difficulties. Resection was incomplete in 2 patients because of upper mediastinum tumour involvement in 1 and microscopic left atrium margin involvement, despite atrium partial resection, in the other. No macroscopic lung or lymph nodes were observed in the 5 patients with CR.

*Table 2. Toxic effects (% of affected patients)**

| | WHO grade | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Haemoglobin | 12 | 17 | 25 | 17 | 29 |
| White cell count | 0 | 4 | 19 | 42 | 35 |
| Neutrophil count | 0 | 0 | 8 | 8 | 84 |
| Platelet count | 24 | 8 | 8 | 28 | 32 |
| Infection | 70 | 0 | 17 | 13 | 0 |
| Haemorrhage | 91 | 3 | 3 | 0 | 3 |
| Nausea/vomiting | 7 | 7 | 44 | 34 | 8 |
| Cardiac function | 94 | 0 | 6 | 0 | 0 |
| Skin | 94 | 0 | 0 | 6 | 0 |

*Haematological toxicity was assessed in 29/33 patients (88%); other toxicities were assessed in all patients. All patients had grade 3 or 4 alopecia.

*Microscopic findings*

In the 5 CR patients, histological analyses of lung and lymph-node surgical samples were negative, resulting in a pTNM staging of T0 N0. In the 13 PR patients who underwent complete resection, pTNM was T1–3 N0 in 3 patients, T1–3 N1 in 6 patients and T1–3 N2 in 4 patients. In the 2 patients who underwent a palliative resection, the pTNM stages were T4 N0. A complete resection was achieved after chemotherapy in the 2 patients who underwent prestudy investigative thoracotomy. Surgery induced no morbidity.

*Survival*

Survival was calculated by the Kaplan–Meier method taking into account the treatment-related death and 2 deaths due to unrelated causes. Mean follow-up was 1 year. Probability of survival was 37% and 30% at 12 and 18 months respectively, with a median survival rate of 10 months. 6 of the 20 patients who underwent resection died. Central nervous system metastases occurred in 4 and were the cause of death (2 patients with CR and 2 with PR). Liver metastases accounted for deaths in 2 patients with PR.

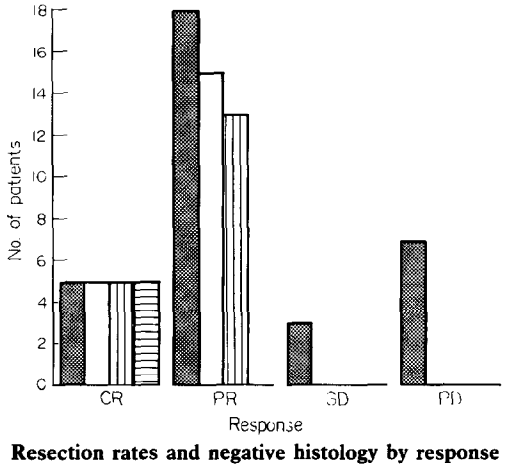


**Fig. 2. Resection rates and negative histology by response type at surgery. Closed column = number of patients in each reponse type, open column = number of overall resections, vertically hatched column = number of complete resections and horizontally hatched column with negative histology.**

## DISCUSSION

This study demonstrated that chemotherapy with ifosfamide/-cisplatin/etoposide was active in locally advanced NSCLC, with a 70% objective response rate and 15% CR rate. Haematological toxicity was cumulative but manageable. In responders surgery was feasible and allowed a 55% complete resection rate and negative histology in all clinical CR patients; surgery-related morbidity and mortality were not observed after neoadjuvant chemotherapy.

The same combination has been used successfully in refractory germ cell cancers [20]. Moreover, ifosfamide is included in many regimens for refractory or metastatic solid tumours such as soft tissue sarcoma [21], brain metastases [22], metastatic non-seminomatous testicular cancer [22], extensive recurrent small cell lung cancer [24] and NSCLC [14–16, 25]. In single-agent trials of NSCLC, cisplatin, ifosfamide and etoposide are among the most active drugs [26]. Moreover, cisplatin and etoposide in combination, which has been used in the treatment of unresectable NSCLC, gave an objective response rate of 38% [18]. In our study, ifosfamide/cisplatin/etoposide gave a higher overall response rate, including a significant number of CRs. However, this higher activity may be partly explained by the fact that patients with locally advanced NSCLC usually have a better performance status and a lower tumour burden than patients included in treatment for unresectable and metastatic NSCLC. Nevertheless, the combination we used is one of the most active regimens when compared with previous studies of locally advanced NSCLC (see, for example, Refs 10–13).

Such studies and our work show that neoadjuvant chemotherapy of locally advanced NSCLC is possible and does not induce major technical difficulties during surgery. However, survival benefit of neoadjuvant chemotherapy cannot be defined since only results from phase II studies are available.

Although careful staging procedures were done before patient inclusion, our study does not demonstrate that neoadjuvant ifosfamide/cisplatin/etoposide can reverse unresectable NSCLC into a resectable condition. Biopsy staging procedures were only used in one-third of the patients; for other patients these procedures were not used because of evidence of gross mediastinal lymph-node involvement which induced main bronchus distortion. However, the rate of CR and the rate of negative histology observed at the time of surgery suggested that resection rate can be improved by neoadjuvant chemotherapy.

The basis has been laid for a phase III randomised comparison of neoadjuvant ifosfamide/cisplatin/etoposide followed by surgery with surgery alone to assess whether enhanced response and resection rates could increase survival of NSCLC patients.


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