Long-Term Results of Neoadjuvant Ifosfamide, Cisplatin, and Etoposide Combination in Locally Advanced Non-Small-Cell Lung Cancer*

Jean-Louis Pujol, M.D.; Maurice Hayot, M.D.; Philippe Rouanet, M.D.; Thierry Le Chevalier, M.D.; and François-Bernard Michel, M.D., F.C.C.P.

Thirty-three patients with T3,N2,M0 or T4,N2,M0, non-small-cell lung cancer (NSCLC) took part in a phase 2 study in an attempt to evaluate the feasibility of neoadjuvant chemotherapy followed by surgery and thoracic radiotherapy. Chemotherapy consisted of daily administration of the following treatment: etoposide, 100 mg/m²; cisplatin, 25 mg/m²; ifosfamide, 1.5 g/m²; and mesna, 1.5 g/m² for 4 days. Three cycles were planned starting every 21 days. Responding patients underwent a thoracotomy in order to attempt a resection and then received a 45 Gy of thoracic radiotherapy. The results of response and resection rates have been published and the present final report deals with the long-term results. Chemotherapy induced a 55 percent partial response rate and a 15 percent complete response rate allowing a complete resection in 55 percent of the patients. Complete remission was histologically confirmed for the five complete responders. Although the median survival was short (10 months), six patients were long-term survivors (3-year survival rate: 19 percent). Survival was significantly influenced by the type of resection: patients for whom a complete resection was possible survived the longest with a median survival three times that of the other patients. Modalities of resection differed according to the results of surgery: 8 of the 15 patients who did not undergo a complete surgical resection experienced a local relapse during the first 18 months of follow-up whereas in the complete resection group, central nervous system metastasis was the main site of relapse. We conclude that the neoadjuvants ifosfamide, cisplatin, and etoposide in patients with locally advanced NSCLC are feasible to use and allow a 19 percent 3-year survival rate. These results are the rationale of an ongoing randomized study comparing neoadjuvant chemotherapy followed by surgery and surgery alone. This study is designed to test whether neoadjuvant chemotherapy improves survival of patients with locally advanced NSCLC.

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Non-small-cell lung cancer (NSCLC) is frequently associated with a metastatic disease at some time during the microscopic stage rather than when it becomes clinically detectable.1 Patients with a locally advanced NSCLC, particularly stage N2, are sometimes considered for surgery, but resection is frequently followed by metastatic relapses.2 There are two underlying problems where local and regional extension in NSCLC is concerned: first, this extension limits the possibility for a surgeon to carry out a complete resection; second, local extension makes the existence of a microscopic metastatic disease predictable. These clinical observations are the rationale for the evaluation of neoadjuvant chemotherapy as an experimental approach.3

In 1987, we started a phase 2 trial of neoadjuvant ifosfamide, cisplatin, and etoposide in patients with locally advanced NSCLC. The response rate, resection rate, and microscopic findings of this study have been published.4 The present report deals with modalities of failures and long-term results.

METHODS

The method of this study has been previously described in detail.4 Briefly, patients of both sexes with locally advanced and histologically proven NSCLC were entered into the study. Prerequisites for inclusion were as follows: age <75 years; World Health Organization (WHO) performance status ≤2; no distant metastasis; weight loss ≤10 percent; respiratory function compatible with surgical resection; normal baseline renal and cardiac functions; baseline neutrophil count ≥2,000/µL; and platelet

NSCLC=non-small-cell lung cancer; TNM=tumor-node-metastasis; UICC=International Union Against Cancer; WHO=World Health Organization.

Key words: feasibility; neoadjuvant chemotherapy; non-small-cell lung cancer (NSCLC); surgery; TNM classification

*From the Chest Department, Hôpital Arnaud de Villeneuve, 34294, Montpellier, France (Dr. Pujol, Hayot, and Michel); The Cancer Institute, Montpellier, France (Dr. Rouanet); and the Institut Gustave Roussy, Villejuif, France (Dr. Le Chevalier). Supported by a grant from the French League Against Cancer and the "Groupement des Entreprises Françaises dans la Lutte contre le Cancer."

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Reprint requests: Dr. Pujol, Maladies Respiratoires, CHU Montpellier, Hôpital Arnaud de Villeneuve, 34059 Montpellier Cedex, France

CHEST / 106 / 5 / NOVEMBER, 1994 1451
Response was achieved in 18 patients (55 percent). Stable disease was observed in three patients and progressive disease occurred in seven patients. Progression during the chemotherapy program consisted of metastases in five patients and local progression in the other two.

Toxicity

The main toxic reaction of ifosfamide, cisplatin, and etoposide chemotherapy was a moderate to severe hematologic one. Ninety-two percent of the patients experienced a grade 3 to 4 neutropenia toxic reaction during the chemotherapy program and 60 percent experienced a grade 3 to 4 thrombopenia (according to the WHO scale). Among them, 10 patients developed a grade 2 to 3 infection. These patients required a hospitalization lasting for 6 days and intravenous antibiotics. Blood transfusions were given to six patients and platelet transfusions were given to four others. One patient died of central nervous system hemorrhage.

Surgery and Microscopic Findings

The results of surgery and pathologic examination of the specimen are shown in Table 1. The overall complete resection rate was 55 percent (18/33). Among them, no macroscopic or microscopic remainders were seen for the five complete responders. Three additional patients were operated on: one open and close and two incomplete resections. No surgery was envisaged for the remaining 12 patients owing to restaging procedure demonstrating an inoperable disease. No additional morbidity was observed after surgery. The frequency of a complete resection did not significantly differ when patients with a pretreatment positive lymph node biopsy specimen were compared with patients for whom lymph node involvement had been demonstrated by CT scan only (66 percent vs 50 percent; \( \chi^2 \): 0.73; NS).

Survival

Median follow-up duration was 16 months (range, 1 to 64 months). One patient was unavailable for

| Table 1—Resection Rate and Negative Histology Following Neoadjuvant VIP |
|--------------------------|------------------|------------------|
| Response to VIP | Complete Resection (%) | Negative Histology (%) |
| CR | 5 | 5 (100) | 5 (100) |
| PR | 18 | 13 (72) | 0 (0) |
| SD | 3 | 0 | 0 |
| PD | 7 | 0 | 0 |
| Global | 33 | 33 (55) | 5 (15) |

*VIP = ifosfamide, cisplatin, etoposide combination; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.
follow-up. Median survival was 10 months. Probabilities of survival at 1, 2, and 3 years were 43, 28, and 19 percent, respectively (Fig 1). In responding and stable patients, median time to progression was 16.7 months (Fig 2). Patients who underwent a complete resection proved to have a significantly longer time to progression and overall survival when compared with patients who underwent either incomplete or no resection (median survival, 20.1 and 6.7 months for the former and latter patient subgroups, respectively; log-rank test: p<0.0001; Fig 3). Histologic subtype, ie, squamous vs others, grade III to IV, hematologic toxicity, and pretreatment weight loss had no significant effect on time to progression and overall survival. The survival of patients who underwent a prestudy mediastinoscopy demonstrating pathologic N2 did not significantly differ when compared with patients for whom only CT scan was carried out to demonstrate stage N2 (median survival, 15.4 and 10 months in the former and the later subgroup, respectively).

Patterns of Relapses

Relapse patterns were studied separately according to the type of resection (Table 2). Among the 18 patients who underwent a complete resection, 6 were alive at time of reporting, 4 died of intercurrent diseases (2 pulmonary embolisms and 2 myocardial infarctions), and 8 experienced a relapse. For these latter patients, distant metastasis was the main modality of relapse with central nervous system representing the unique site in four.

Among the 15 patients for whom resection was either incomplete or not done, none survived more than 18 months after the induction therapy, one died after cycle 1 of central nervous system hemorrhage, and 13 experienced a relapse. Local progression was the main modality of relapse for those patients (8/15). Conversely, brain metastasis seems to be a rare event in this subgroup as only one patient had this modality of relapse. All six long-term survival patients have had a complete resection and are free from disease at time of reporting (Table 3). Three of them have had biopsy-proven stage-N2 found by prestudy mediastinoscopy. Half of the long-term survivors responded completely to chemotherapy and the others were partial responders. In all cases, results of the pathologic examination of the resection showed normal nodal status.

DISCUSSION

This study shows that neoadjuvant ifosfamide, cisplatin, and etoposide is an active combination in patients with locally advanced NSCLC inasmuch as it induced complete pathologic response in 15 percent of the patients and allowed a complete resection in 55 percent. This antitumor activity is associated

![Figure 1. Overall survival.](image1)

![Figure 2. Time to progression.](image2)

![Figure 3. Survival according to the type of resection (complete resection vs incomplete or no resection).](image3)
with a 19 percent 3-year survival. The modality of relapse differs when patients who underwent a complete resection are compared with others, the central nervous system remaining the first site of failure in the former group.

Neoadjuvant chemotherapy was tested in patients with NSCLC in an attempt to increase the resectability of the tumor and to treat the microscopic metastatic disease known to be responsible for the majority of failures in surgically treated patients. Several published trials have been reviewed extensively.1,10 Most of them are feasibility studies in stage III NSCLC. Obviously, the heterogeneity of eligibility criteria from one study to another prevents general conclusions on the usefulness of neoadjuvant chemotherapy. In addition, the majority of the studies, including the one reported herein, have been designed as phase 2 trials and, therefore, they cannot answer the following questions. Is the operability of patients with NSCLC increased by neoadjuvant chemotherapy? Is overall survival improved by this approach? However, it is possible to conclude that neoadjuvant chemotherapy has an antitumor activity: most studies report a 60 percent objective response rate, including a significant number of complete responses and a 30 percent complete resection rate. Neoadjuvant chemotherapy does not increase morbidity after surgery except when it is combined with preoperative radiation therapy.1,10

The results of our study show similar rates of chemotherapy-induced tumor responses, complete pathologic responses, and complete resections. The staging procedure we used could be discussed. In the literature, some studies used a radiographic definition of mediastinal lymph node enlargement (clinical N2)11,12 whereas others used a strict pathologic definition of this involvement.13,14 Although a real comparison of these two groups of studies is not possible for methodologic reasons, there is no major difference when resection rates and survivals are considered. In our study, we decided to avoid mediastinoscopy for patients with bulky N2 on CT scan and to determine N2 disease pathologically in the other cases. We observed no difference in resection rate and survival when these two groups were compared. In addition, three of six of the long-term survival patients had a biopsy-proven N2 stage tumor at time of inclusion.

The analysis of survival in our study showed that long-term survival can be achieved in patients with N2 disease receiving neoadjuvant chemotherapy. Median survival was calculated as 10 months by the Kaplan-Meier method and suggested a weak advantage of neoadjuvant ifosfamide, cisplatin, and etoposide. However, the median survival is only a rough indicator of prognosis, particularly in a small size population and the 3-year survival rate might be a better variable to evaluate a study. The 19 percent 3-year survival observed in our study can be regarded as sufficiently favorable to consider our protocol as feasible. A clear survival advantage has been observed for patients who underwent complete resection. However, it is not possible to assume that surgical excision is the only reason for such a result and some other factors, including response to chemotherapy, might be considered.

In the published studies, median survival varied from 8 to 24 months. This wide range might be explained by (1) true differences in efficacy between protocols, and (2) heterogeneity of eligibility criteria. When available, long-term survival reports show that a 15 percent 3-year survival rate can be expected for patients who benefit from neoadjuvant chemotherapy. These results are not a proof of the chemotherapy efficacy but deserve further randomized studies.

<table>
<thead>
<tr>
<th>No.</th>
<th>Histology*</th>
<th>Pretreatment TMN</th>
<th>Response to IT</th>
<th>Type of Surgery</th>
<th>pTN</th>
<th>Operative Histology</th>
<th>Follow-up, mo</th>
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</thead>
<tbody>
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<td>1</td>
<td>SQC</td>
<td>T3,N2,M0</td>
<td>Partial</td>
<td>Pneumonectomy</td>
<td>T2,N0</td>
<td>Positive</td>
<td>38</td>
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<tr>
<td>2</td>
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<td>Complete</td>
<td>Lobectomy</td>
<td>T0,N0</td>
<td>Negative</td>
<td>39</td>
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<tr>
<td>3</td>
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<td>T3,N2,M0</td>
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<td>4</td>
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<td>T1,N0</td>
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<tr>
<td>6</td>
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<td>Complete</td>
<td>Pneumonectomy</td>
<td>T0,N0</td>
<td>Negative</td>
<td>63</td>
</tr>
</tbody>
</table>

*ADE = adenoma; IT = induction therapy; pTN = pathologic tumor node; LCC = large-cell carcinoma; SQC = squamous cell carcinoma.
†Biopsy specimen proven N2.
designed to test the effectiveness of neoadjuvant chemotherapy in NSCLC. In this setting, a possible study design to determine the survival advantage of neoadjuvant chemotherapy might be to randomize patients with stage N2 NSCLC between neoadjuvant chemotherapy followed by surgery and surgery alone. A recent study investigating this comparison concluded that neoadjuvant chemotherapy increases the median survival of stage IIIa NSCLC.15

In March 1990, we started a randomized phase 3 trial based on a similar design. The aim of this study is to determine whether enhanced response and resection rates could increase survival of patients with NSCLC treated by ifosfamide, cisplatin, and etoposide neoadjuvant chemotherapy. Other trials based on alternative methods of randomization are also ongoing and one could expect that these studies could define the place for neoadjuvant chemotherapy in NSCLC.

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