Benefits of Neoadjuvant Chemotherapy in NSCLC*

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There is a significant potential benefit for induction chemotherapy in the management of non-small cell lung cancer (NSCLC). The real extent of such benefit is difficult to assess on the basis of available data owing to the intrinsic limitations of phase II studies. In fact, in most studies on neoadjuvant chemotherapy, the aim of the treatment (local control vs systemic effect) is often unclear, the eligibility criteria poorly defined, and pretreatment staging inadequate. Consequently, the interpretation of the results of such studies has proved difficult. This article examines the critical role of thoracic surgeons in the selection, staging, and optimal treatment of patients enrolled in neoadjuvant studies, and also in monitoring the quality of data and providing adequate specimens for concurrent biologic research. Within the framework of controlled trials, with proper methods and minimum toxic reactions, induction chemotherapy may be offered in the future to a large number of patients and eventually combined with long-term adjuvant/chemopreventive strategies. (CHEST 1996; 109:963-101S)

The overall proportion of patients amenable to curative surgery has not changed significantly over the last 20 years. Complete resections with adequate surgical margins only account for 20 to 30% of all primary lung cancers in the United States and even less in Europe. In the vast majority of cases, surgery is not possible because of anatomic extension or not advisable because of the high chance of occult metastases. Even for clearly resectable cases, the 5-year survival is only 60% for stage I, 40% for stage II, and 20% for limited stage IIIA.1,2 For mediastinoscopy-positive N2 disease, the 5-year survival falls to 5 to 10%. For more advanced stages, surgery alone yields no chance of cure. In fact, in historic series, the 5-year survival after resection for bulky N2-3 disease and T4 tumors invading mediastinal structures, such as superior vena cava, aorta, myocardium, or esophagus, is 0%.2,3 Analogously, median survival in the presence of cytologically positive pleural effusion is shorter than 6 months.4

It is obvious from these survival figures that the overwhelming majority of patients with non-small cell lung carcinoma (NSCLC) would require an effective systemic treatment to make surgery and/or radiotherapy successful.

Postoperative Chemotherapy

Early randomized trials testing alkylating agents as adjuvant chemotherapy after complete resection resulted in similar, if not significantly shorter, survival for patients receiving systemic therapy.5,6 The introduction of cisplatin-based regimens produced some encouraging results through the experience of the Lung Cancer Study Group. Adjuvant chemotherapy with cyclophosphamide, doxorubicin, and cisplatin (CAP) regimen improved the disease-free survival of patients with stage II to IIIA and incomplete resection.7-9 In stage I, the results of the Lung Cancer Study Group trial were negative,10 while another smaller trial showed only a marginally significant benefit.11 A major problem with these trials, however, was treatment compliance, as only 50 to 60% of patients received postoperative chemotherapy as planned.

A recent meta-analysis of eight trials from Medical Research Council demonstrated a statistically significant advantage for cisplatin-based chemotherapy arms, with an overall 13% reduction in the risk of death and a 5% improvement of survival at 5 years (unpublished data; R. Souhami, MD, 1994).

In conclusion, there is evidence of a beneficial effect of systemic adjuvant treatment, but the extent of this benefit with the available regimens is small, probably in the order of a 5 to 10% gain on long-term survival.

Preoperative Chemotherapy

Induction chemotherapy or chemotherapy/radiotherapy has been reported as improving the chance of curative resection of advanced or marginally resectable NSCLC (stage IIIA-B). The long-term survival in phase II studies has reached 18%, compared with 9% of historic control subjects.12,13 One must consider, however, that in the group of bulky N2 tumors, the 5-year survival after induction chemotherapy was only 4%. It appears that a higher resectability rate and more
favorable long-term survival was achieved in those patients who responded to the induction treatment.

Recently, two randomized trials have demonstrated a significant improvement in survival of patients receiving induction chemotherapy for stage IIIA NSCLC. These results are extremely important and are discussed in detail elsewhere in this journal. The main limit of both trials is the small number of randomized patients, emphasizing the problem of clinical heterogeneity of stage III disease. This may explain the dismal survival observed in the surgical arm of one of the two trials.

From the surgeon’s point of view, preoperative or neoadjuvant chemotherapy may be more appealing than postoperative therapy in many respects. First of all, it may be more effective on occult micrometastases and prevent tumor progression due to perioperative immunosuppression and release of growth factors related to wound healing. Chemotherapy may be better tolerated by the patient before surgery. In patients with marginally resectable disease, the regression of primary tumor and/or nodal metastases may facilitate surgery and reduce the required resection volume. Moreover, clinical and pathologic response can be used to select those patients eligible for further treatment (surgery, radiotherapy, or chemotherapy).

The reason why many thoracic surgeons are still skeptical about the ultimate value of neoadjuvant chemotherapy lies in the weak design of most phase II studies in which the aim of the treatment (local control vs systemic effect) is often unclear, the eligibility criteria poorly defined, and pretreatment staging of the enrolled patients inadequate. Consequently, the interpretation of the results of such studies has proved difficult.

**Critical Aspects of Induction Chemotherapy**

**Importance of Staging and Surgical Management**

In designing clinical trials for stage III lung cancer, the assessment of both tumor extent and the patient’s general condition are of paramount importance. A good study design will inevitably require considerable commitment from the thoracic surgeon, in terms of careful selection of patients suitable for multimodality treatment, choice of adequate resection volume, and optimal surgical technique to minimize morbidity and mortality. As a matter of fact, studies that require good clinical staging are more likely to attract the interest and participation of good thoracic surgeons.

There is a basic biologic prejudice on the medical side that the quality of surgery has a limited impact on the outcome of lung cancer. In the trial design, such a prejudice is expressed by the great emphasis in assessing even minimal differences in chemotherapy schedules, toxicity, and response compared with the very limited information provided on surgical management.

In real clinical practice, the variation in long-term survival related to surgical performance, as a combination of early mortality and local or regional recurrence, may well exceed the 10% difference that one can reasonably anticipate as a benefit of chemotherapy. It is likely, in fact, that accurate staging will lead to more accurate surgery. For this reason, whenever different multimodality therapies are compared in prospective randomized trials, the quality of each individual modality should be properly assessed and monitored, even if the final analysis will be made according to the intention to treat. In this particular setting, it is essential to assess that surgical performance is similar in both arms.

Recent developments in molecular biology and cytogenetics offer new instruments to investigate patient and tumor status prior to treatment, and the extent of biologic changes induced by chemotherapy/radiotherapy. The potential scientific implications are unlimited, and in practical terms, an immediate field of application would be the testing of new drugs. Again, this underlines the importance of systematic surgical sampling, to provide the laboratory with adequate and consistent specimens of various tissues, before and after induction therapy.

Until now, clinical trials on neoadjuvant chemotherapy have included a highly heterogeneous mixture of stage IIIA and IIIB, with the assumption that an anticipated 5-year survival of 5 to 10% was low enough to justify neoadjuvant chemotherapy and to demonstrate a benefit in case of effective control of distant disease. Within the large group of patients with stage III NSCLC, however, survival ranges from 0 to 50% and for the purpose of clinical trials it is essential to identify those patients who clearly have unresectable disease, those who have resectable disease but with poor prognosis, and the patients who have resectable disease with a marginal or good prognosis.

**Main Prognostic Subgroups**

Patients with massive N2 disease, including multiple confluent or extranodal metastases, contralateral metastases, or suprACLavicular metastases have to be considered as having surgically nonresectable disease (Fig 1). The same holds true for massive T4 disease infiltrating mediastinal structures such as superior vena cava, aorta, myocardium, or esophagus. There is no indication for primary surgery in these patients, as 5-year survival in historic series is virtually 0%.

A second prognostic subgroup is represented by patients with mediastinoscopy-positive N2 disease involving multiple stations, with N2 disease crossing the
midline, or T3 tumors with one mediastinal metastasis (Fig 2). Patients with negative mediastinoscopy but intraoperative detection of metastases to multiple mediastinal stations belong to the same group. These cases are technically suitable for complete resection, but the prognosis is very poor. The 5-year survival in historic series is 5 to 10% after primary surgery, and these figures are similar, if not worse, than the ones achieved by radiotherapy alone or chemotherapy/radiotherapy.

A third group is represented by patients with limited mediastinal spread (Fig 3). This includes patients with negative mediastinoscopy or normal mediastinal appearance at CT scan and limited intraoperative N2 disease or microscopic nodal involvement at final histopathology report. Patients belonging to the same group include those with abnormal cervical mediastinoscopy results or anterior mediastinotomy but restricted to a single mediastinal station proximal to the primary tumor, such as R4 for right upper lobe tumors or L5-6 for left upper lobe tumors. These patients are indeed surgical candidates, although the prognosis may be defined as marginal. In fact, the 5-year survival is in the order of 20 to 25%.

A further subset of stage III NSCLC is represented by T3N0 tumors (Fig 4). These are patients with good prognosis in whom surgery alone can achieve a 50% survival at 5 years.

Eligibility for Neoadjuvant Trials

In the United Kingdom, nearly 10% of the 20,000 new cases of NSCLC diagnosed each year would be considered operable, but only a small minority of these patients are currently recruited into prospective studies. This 10% could be a ready source of patients for good randomized trials on induction chemotherapy, provided that more surgeons became involved in the design and management of such trials. Alternatively, a closer cooperation among lung physicians, medical oncologists, radiotherapists, and thoracic surgeons could ultimately increase the total number of patients who receive a potentially curative treatment. A large proportion of these patients may be eligible for randomized trials on the efficacy neoadjuvant chemotherapy, provided that their general fitness and stage of disease has been properly assessed.

There is still a requirement for studies comparing surgery vs surgery plus chemotherapy in patients with resectable stage IIIA tumors with poor or marginal prognosis, because the extent of the benefit of induction chemotherapy has not been settled by the avail-

**Figure 1.** Patients with stage III lung cancer that is not surgically resectable.

**Figure 2.** Patients with resectable disease with poor prognosis.

**Figure 3.** Patients with resectable disease with marginal prognosis.
able data. In other words, for limited or single-stage N2 disease, the question of whether survival after complete surgical resection can be significantly improved by neoadjuvant chemotherapy is still open. We need larger trials in which the surgical control arm is a good representative of this population and the 5-year survival falls in the expected range of 10 to 15%.

For patients with unresectable NSCLC, the question is obviously whether surgery adds anything to primary chemotherapy/radiotherapy. There are a few prospective studies ongoing that will hopefully clarify this matter.

In the pretreatment staging of patient candidates for induction chemotherapy, an objective limitation is represented by the fact that cervical mediastinoscopy and even anterior mediastinotomy cannot reach all the mediastinal stations which may need to be biopsied on the basis of CT scan. New techniques, such as video-assisted thoracoscopy (VATS) can now be used to implement the staging modality and select those patients who are eligible for neoadjuvant chemotherapy. The efficacy of VATS in achieving tissue diagnosis of critical mediastinal areas, suspicious lung metastases, or pleural effusions, may well be evaluated in the framework of new prospective trials. In fact, there is a sound biologic rationale to enroll even patients with stage I and II disease in such trials. The matter of accurate pretreatment staging is then essential to test different types of induction therapy according to the different risk of relapse or to stratify randomization within the same trial design.

**Future Studies**

**Biologic Assessment of Risk**

Biologic definition of high-risk subjects has become one of the crucial aspects of clinical research. Recent developments in cytogenetics and molecular biology have demonstrated that it is possible to identify specific genetic abnormalities in the various phases of upper respiratory and digestive tract carcinogenesis. Such abnormalities can be interpreted as markers of cumulative genetic damage, but also as expression of individual susceptibility to cancer. It is therefore of extreme interest to investigate the use of specific biologic markers to predict a different individual outcome (recurrence, new primary malignancies, survival) for each patient and decide optimal adjuvant treatments after complete resection.

The discovery of chromosomal rearrangements in lung cancer, initially observed in cell lines, has been extended to the systematic testing of fresh tumor samples, thus enabling the correlation with clinical features and prognosis. Deletions, translocations, or polysomies have been identified with higher frequency on specific chromosomes, and now it is possible to assess them on paraffin blocks by in situ hybridization.

Widespread application of molecular biology techniques has demonstrated the activation of dominant oncogenes (myc, ras, EGFR, neu) and inhibition of suppressor oncogenes (rb1, p53, rar-β), with a high level of correlation with chromosomal abnormalities. The development of specific monoclonal antibodies, suitable for the analysis of paraffin-embedded material, makes it possible to evaluate retrospectively large clinical series, with long-term follow-up.

The potential prognostic value of biologic markers has been addressed by a number of retrospective studies focused on group A antigens or their precursors, p53 protein, c-erbB-1/EGFR and c-erbB-2/neu oncogenes, bcl2 gene, and K-ras mutation on codons 12 and 13. Preliminary reports, however, have been based on small retrospective series of highly selected and sometimes poorly staged cases, and in some instances (p53, bcl2, group A), the initial results could not be confirmed by further studies.

A major issue is now to confirm the prognostic value of biologic markers on larger series of patients, possibly derived from prospective trials in which the stage and treatment parameters as well as the long-term outcome have been independently assessed. As an example, we are presently evaluating 600 consecutive cases of resected stage I NSCLC in which the expression of specific antigens associated with differentiation (blood group antigens and precursors: group A, Lewis-a, Lewis-y), proliferation (EGFR, p185 HER2, p53, Bcl2), angiogenesis, and metastatic potential (laminin receptor) is concurrently tested on the tumor and on the normal bronchus by the use of monoclonal antibodies.
Short-term Chemotherapy

Prospective randomized trials focused on short-term (two to three cycles) induction chemotherapy may be designed to recruit a larger number of patients eligible for curative surgery. If the performance status and pulmonary function are adequate, even patients with stage I and II disease may be considered eligible for preoperative treatment in a controlled setting.

Patients with more advanced tumors may be offered the chance of induction treatment, including new drugs. Substances such as CPT-11, docetaxel, gemcitabine, paclitaxel, topotecan, and vinorelbine have shown a clear antitumor activity in NSCLC. They could be tested in combination with cisplatin and other agents in randomized phase II studies. The neoadjuvant design would enable an early screening of the activity of new agents, with a solid end point represented by pathologic response.

Long-term Chemoprevention

Early chemoprevention trials have demonstrated that treatment with high-dose retinol or 13-cis retinoic acid significantly reduced the risk of new primary tumors in patients with previously treated stage I lung cancer or head and neck cancer. Retinoids and other new preventive agents should be used in optimal combination schedules, with the aim of counteracting late stages of lung carcinogenesis and preventing the occurrence of secondary primary malignancies. To improve the likelihood of success, chemoprevention can be offered to patients at higher risk, on the basis of genetic lesions detectable in normal epithelium.

In addition to the genetic abnormalities already discussed, a new promising marker is represented by the gene coding for the receptor of retinoic acid β (rar-β), which is located on the distal region of the short arm of chromosome 3 (3p24). This gene is directly involved in the activity of retinoids. Reduced expression of rar-β has been demonstrated in cancer cell lines and human lung cancer. Our recent research, conducted in cooperation with M.D. Anderson Cancer Center, showed that rar-β is not expressed in 50% of dysplastic lesions and normal bronchial epithelium of lung cancer patients, whereas the expression of the other receptors (rar-α-γ) is not altered. All the above data suggest that rar-β may act as an onc suppressor gene in lung carcinogenesis, being modulated by retinoid administration.

In randomized trials testing new adjuvant strategies, it may be appropriate to incorporate long-term chemoprevention agents as part of the multimodality treatment.

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