Current Development of Adjuvant Treatment of Non–Small-Cell Lung Cancer

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Abstract

Although radical surgery remains the mainstay therapeutic modality for early-stage non–small-cell lung cancer (NSCLC), long-term survival of patients with completely resected NSCLC tumors remains suboptimal. Globally, the 5-year survival rate of patients who undergo complete surgical resection is in the range of 40%-50%. The majority of postsurgical relapses are represented by distant metastases, with the risk of a local recurrence being < 10%. Postoperative treatments, including chemotherapy, radiation therapy, or both, have been widely evaluated during recent decades. After almost 2 decades of disappointing results, the positive outcomes of 3 randomized studies have recently generated new hopes for a significant impact on survival by adjuvant chemotherapy. The 2 largest randomized studies of adjuvant chemotherapy in all stages (I-IIIA) of completely resected NSCLC that were adequately powered to detect small differences in survival yielded partially conflicting results but indicated that, if any benefit from adjuvant chemotherapy exists, it is approximately 5% at 5 years, as previously anticipated by a metaanalysis. More recently, 2 other randomized studies in selected subgroups of patients (one selectively performed in stage IB disease, the other in stage IB/II disease) indicate an unexpected significant benefit of approximately 15% at 5 years. Potential confounding factors may have contributed to such a significant benefit. A feature common to all these trials is the suboptimal therapeutic compliance to adjuvant chemotherapy, suggesting the need for careful selection of patients to be considered for adjuvant treatment. Genomic- and proteomic-driven chemotherapy as well as molecularly targeted therapies may represent additional areas of near-future clinical investigations.

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Introduction

Surgery represents the main curative therapeutic approach for early-stage disease (stages IA-IIB) non–small-cell lung cancer (NSCLC). Unfortunately, these cases represent only a minority (20%-25%) of cases of NSCLC. Specific groups of patients with stage III disease also benefit from pulmonary resection, usually in combination with other treatment modalities. The use of a systemic therapy in completely resected NSCLC is reasonably justified by follow-up studies after radical resection that have shown predominance of distant failures over local recurrences and some clinical and pathologic evidence of early microdissemination of disease at the time of surgery.

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Pattern of Relapse After Complete Resection for Early-Stage NSCLC

Long-term survival in NSCLC following surgical resection is stage-related, but even in stage IA, one third of patients will relapse and die of disease within 5 years.[1] The majority of these relapses are distant metastases, with the risk of a local recurrence after complete resection being < 10%. The brain is the most common site of metastatic recurrence, followed closely by bone, ipsilateral and contralateral lung, liver, and adrenals. More than 80% of recurrences occur within 2 years from the time of radical surgery.[2]

The rate of recurrence for patients with stage II disease is higher than in stage I; > 50% of resected stage II disease can be expected to relapse and most recurrences are distant. The pattern of recurrence may differ by histology with more local recurrences seen for patients with squamous cell carcinoma and more distant metastases seen in patients with adenocarcinoma.[3-6]

The Rationale for Adjuvant Treatments

Following complete resection, tumor load, if any, is theoretically minimal. The relatively small number of residual neoplas-

tic cells present in micrometastatic disease should contain few chemotherapy- or radiation-resistant clones. The Gompertzian model of tumor growth and regression fits experimental and clinical data of most human solid cancers—if the assumptions are effectively correct, when the tumor is clinically undetectable, its growth rate should be at its largest, and, although the numeric reduction induced by cytotoxic chemotherapy is small, the fractional cell kill from an effective dose of chemotherapy should be higher.[7] In addition, pathologic staging allows better prediction of prognosis and facilitates the comparison of treatment results between different trials.

Adjuvant Radiation Therapy

For a long period of time, postoperative thoracic radiation therapy (RT) was the preferred adjuvant treatment. Results regarding its potential role have been reported from a large number of retrospective and prospective studies. Nine of these studies, collecting individual data from 2128 patients, have been included in the postoperative RT (PORT) metaanalysis and indicated PORT as a treatment with significant detrimental effect on survival. Data indicated a 21% relative increase in the risk of death, equivalent to an absolute detriment of 7% at 2 years, reducing the survival rate from 55% to 48% with PORT (P = 0.001; hazard ratio [HR], 1.21; 95 CI, 1.08-1.34). Subset analyses suggested a trend toward greater negative effects for lower nodal status (P = 0.016 for nodal status 0-2) and earlier stages of disease (P = 0.0003 for stage I-III), with a distinct survival detriment for stage I disease and a clear lack of benefit or detriment for stage III disease.[8]

Most of the studies included in the PORT metaanalysis incorporated patients treated with older technology (cobalt 60) and different dosimetry, and these outdated parameters may be partially responsible for the higher mortality rate observed in the RT group attributable to an excess of intercurrent deaths. The use of newer technologies and improved dosimetry may prove to be effective, as more recently suggested in a retrospective review.[9] In addition, in the PORT metaanalysis, there were no sufficient data on mediastinal lymph node dissection and the surgical procedure varied greatly among studies and centers. Consequently, the role of RT in patients with N2 disease remains unclear, as no definitive conclusions can be drawn from the PORT metaanalysis.

A study not included in the metaanalysis was subsequently reported and aimed to investigate the value of adjuvant postoperative external-beam RT in patients with radically resected NSCLC (pT1-3 pN0-2) compared with patients with resected NSCLC without adjuvant external-beam irradiation. In that study, 155 patients were randomized to surgery alone (n = 72) or surgery followed by PORT (n = 83). With a median follow-up of 3.6 years, there was no statistically significant difference in the overall 5-year survival rate (20.4% with surgery alone vs. 29.7% with surgery plus PORT; P > 0.05). A subgroup analysis conducted separately for each pathologic stage did not result in any significant survival benefit for PORT when compared with surgery alone at 5 years (pN0 and pN1) or 2 years (pN2).[10] New randomized studies are awaited to assess the impact of adjuvant RT on local control and survival.

However, in consideration of the pattern of recurrence and relapse observed in patients who had previously completely resected early-stage NSCLC, it is quite unlikely that a local treatment such as postoperative RT—although it may potentially improve local control rate—will be able to significantly modify the survival of patients who have surgically resected early-stage NSCLC. Only the use of an effective systemic treatment that will eradicate micrometastatic clones has the potential to significantly affect survival. Theoretically, the combination of thoracic RT, delivered through the latest-generation RT machines, and platinum-based combination chemotherapy allows the optimization of local control and extrathoracic micrometastatic disease.

History of Adjuvant Chemotherapy in Early-Stage NSCLC

The history of adjuvant chemotherapy in completely resected NSCLC began in the early 1960s and 1970s with trials testing the roles of alkylating agents and nonspecific immunotherapies (mainly levamisole and Bacillus Calmette-Guérin) that uniformly failed to demonstrate any survival benefit; occasionally, a detrimental effect was observed.[11] All the drugs used in these studies had shown very limited or no activity in advanced NSCLC.

How does one select the most appropriate treatment to be used in the adjuvant setting? Realistically, no definitive rules have been established, but the chosen treatment should at least be proven active in advanced-stage disease and be associated with good tolerability.[12]

In the 1980s, the role of cisplatin-based combinations was extensively tested. These studies may be grouped into 2 series. Most of these studies included patients with predominantly stage III NSCLC, and CAP (cyclophosphamide/ doxorubicin/cisplatin) was more commonly investigated. All these studies failed to show any improvement in median and long-term survival.[13-17]

Two other studies testing the role of cisplatin-based chemotherapy were performed, mostly in patients with stage I disease.[18,19] In one of these studies, 110 patients with completely resected T1 3N0 NSCLC were randomized to receive CAP or no additional therapy. After 10 years of follow-up, survival was significantly better in the experimental arm than in the control arm (61% vs. 48%, P = 0.05).[18] In the second study, eligible patients with completely resected stage I NSCLC were classified by known prognostic factors and randomly assigned to receive 4 courses of CAP at 3-week intervals beginning on day 30 after surgery or no treatment. The CAP regimen consisted of 400 mg/m^2 cyclophosphamide, 40 mg/m^2 doxorubicin, and 60 mg/m^2 cisplatin. Stratification by prognostic factors included histology, white blood cell count before surgery, and Karnofsky performance status before surgery. After a mean follow-up of 3.8 years, there were no differences in time to recurrence or overall survival (OS; not stratified by histology) between the 2 groups, even when analyses were adjusted for prognostic variables.[19]

Findings among these studies include variation in sample size, overestimation of the potential benefit of adjuvant chemotherapy, imbalance in patient and treatment characteristics (ie, incomplete mediastinal lymph node dissection), and, for a majority of these studies, impossibility of reaching the planned

Table 1 Recent Randomized Clinical Studies of Platinum Agent–Based Adjuvant Chemotherapy in Completely Resected NSCLC[22-26]

Study	Site	Disease Stage	Chemotherapy Regimen	Control Arm	Planned Accrual	Actual Accrual	Trial Outcome
ANITA I	International	I, II, IIIA	**Cisplatin/Vinorelbine** for 4 cycles	Observation	800	831	Pending
Intergroup 0116	United States	T1-3 N1/2	**Cisplatin/Etoposide** for 4 cycles	RT	462	488	Negative
JCOG	Japan	IIIA N2	**Cisplatin/Vindesine**	Observation	200	119	Negative
IALT[22]*	International	I, II, IIIA	**Cisplatin/Etoposide** or Vinca Alkaloids for 3-4 cycles	Observation	3300	1867	Positive
ALPI[23]*	Italy/Europe	I, II, IIIA	**Cisplatin/Mitomycin C/Vindesine** for 3 cycles	Observation	1200	1209	Negative
BLT[24]*	United Kingdom	I, II, IIIA	**Cisplatin/Etoposide** or Vinca Alkaloids for 3 cycles	Observation	481	381	Negative
CALGB 9633[25]	United States	IB	**Carboplatin/Paclitaxel** for 4 cycles	Observation	504	344	Positive
NCIC BR.10[26]	Canada	T2 N0 T1/2 N1	**Cisplatin/Vinorelbine** for 4 cycles	Observation	640	482	Positive

*Sequential thoracic RT allowed according to each institution policy; 13% received RT in both arms of the study.
Abbreviations: ANITA = Adjuvant Navelbine International Trialist Association; BLT = Big Lung Trial; JCOG = Japanese Clinical Oncology Group

accrual. These flaws possibly reflect negative attitudes of thoracic surgeons toward adjuvant chemotherapy, and the modern multidisciplinary approach to patients with early-stage NSCLC may be a way to overcome this problem.

In addition, most of the trials' dose delivery, including total dose and dose intensity of chemotherapy agents, was often reported to be inadequate, with an average of 50% of patients receiving the full course of treatment.

Recent Studies of Adjuvant Chemotherapy in NSCLC

In 1995, a metaanalysis performed with different subgroups of patients with NSCLC receiving chemotherapy analyzed 8 cisplatin-based adjuvant chemotherapy trials in 1394 patients and demonstrated a 13% reduction of the risk of death, which was close to the borderline of statistical significance (P = 0.08). Similarly, there was a 6% reduction in the risk of death in patients treated with PORT and cisplatin-based chemotherapy compared with patients who received only PORT (P = 0.46). Conversely, adjuvant chemotherapy with long-term alkylating agents was significantly detrimental.[20]

These findings failed to affect clinical practice, not because the absolute gain was too small, but because such an estimate was still imprecise, ranging from a 1% detriment to a 10% benefit. In addition, the heterogeneity of surgical procedures and the difference in staging modalities strongly limit the applicability of the results of this metaanalysis. This was not the case, for example, for breast cancer adjuvant chemotherapy, the similarly narrow 6% benefit of which in 10-year survival rate emerged from a metaanalysis involving approximately 75,000 patients, with 31,000 recurrences and 24,000 deaths.[21]

This statistically insignificant benefit in 5-year survival of the previously mentioned NSCLC metaanalysis generated enough enthusiasm to prompt the planning of several randomized studies, all platinum agent–based (with or without thoracic RT) in completely resected NSCLC of stages I-IIIA (Table 1).[22-26]

The first study published was an Eastern Cooperative Oncology Group (ECOG) trial in which patients with clinical stage II/IIIA NSCLC after complete resection received RT alone or concurrent chemotherapy/RT. Overall toxicity was higher in the chemotherapy/RT group, but no difference was seen in efficacy outcomes.[27] This study was criticized for the small sample size and for the absence of a pure control arm.

The studies in Table 1 are worthy of initial considerations. First, among these studies there is a huge difference in the sample size calculation, from < 500 patients to > 3000, to observe the same therapeutic effect in the same patient population. Second, some of these studies tested the role of adjuvant chemotherapy in all stages of resected NSCLC, whereas others addressed the same question to specific and well-defined subgroups of patients. Third, the only 2 trials designed to observe a reasonable survival advantage in the range of that previously described in the metaanalysis were the Adjuvant Lung Project Italy (ALPI) study and the International Adjuvant Lung Trial (IALT).[22,23]

The ALPI trial, conducted in 70 Italian centers and 7 European institutions affiliated with the European Organization for Research and Treatment of Cancer (EORTC), randomized patients surgically staged with stages I, II, and IIIA NSCLC to receive MVP (mitomycin 8 mg/m^2 on day 1, vindesine 3 mg/m^2 on days 1 and 8, and cisplatin 100 mg/m^2 on day 1 every 3 weeks for 3 cycles) or no chemotherapy.[23] Delivery of PORT (total dose 50-54 Gy in 5-6 weeks, beginning ≥ 4 weeks after the completion of chemotherapy) was left to the policy of participating centers and randomization was stratified accordingly (Table 2).[22,23]

Between January 1994 and February 1998, 1209 patients were randomized. After a median follow-up of 64.5 months, differences in progression-free survival (PFS; HR, 0.89; P = 0.144) and OS (HR 0.96; P = 0.585) were not statistically significant. Only 69% of patients received the 3 full MVP cycles with or without dose adjustments or omissions. On multivariate analysis, only stage and sex emerged as independent prognostic factors. Moreover, there was no good evidence of differential effect of chemotherapy in the different subgroups of patients; in stage I, II, and IIIA disease, the HRs for survival were 0.97 (95% CI, 0.71-1.33), 0.80 (95% CI, 0.60-1.06) and 1.06 (95% CI, 0.82-1.38), respectively (for interaction, P = 0.52). Similar figures were found for PFS: HRs of 0.89 (95% CI, 0.66-1.19), 0.78 (95% CI, 0.60-1.03), and 0.94 (95% CI, 0.73-1.21), respectively. It is remarkable to observe that, in the subgroup of patients with stage II NSCLC, although the HR

Table 2 Patient Characteristics of the IALT and ALPI Studies[22,23]

Characteristics	IALT[22]		ALPI[23]*	
	Chemotherapy (n = 932)	Control (n = 935)	Chemotherapy (n = 472)	Control (n = 465)
Median Age	59 Years	59 Years	61 Years	61 Years
Pathologic Stage				
I	36%	37%	39%	38%
II	25%	24%	31%	34%
IIIA	39%	39%	29%	28%
Histology				
Squamous cell	46%	47%	51%	49%
Non–squamous cell	54%	53%	49%	51%
Pneumonectomies	35%	35%	24%	26%
Complete Lymph Node Dissection	Not Reported		55%	53%
Postoperative RT	30%		43%	43%
Receiving Planned RT	70.4%	84.2%	74%	89%
Median Follow-up Time	56 Months		56 Months	

*From the final analysis, 108 patients from one center were excluded (54 in each arm) because of serious concerns about data integrity.

was not statistically significant, a 10% survival advantage at 5 years for chemotherapy-treated patients was reported.[23]

In this trial, the choice for a triplet combination was suggested by the positive data reported from a trial comparing 3 chemotherapy regimens in patients with advanced NSCLC[28] and by the efficacy of the MVP regimen in the neoadjuvant setting.[29] In patients with stage IIIA NSCLC, triplet combinations were used as induction regimens in 2 small randomized phase III trials that showed a clinically meaningful superiority of the combined approach over surgery alone.[30,31]

The other large worldwide randomized trial, the IALT trial, was aimed at determining the impact on OS of a chemotherapy regimen including cisplatin (80-120 mg/m^2) and a vinca alkaloid (vindesine 3 mg/m^2 weekly, vinblastine 4 mg/m^2 weekly, or vinorelbine 30 mg/m^2 weekly) or etoposide (100 mg/m^2 daily for 3 consecutive days) compared with no chemotherapy after complete surgical resection in patients with stage I-III NSCLC[22] (Table 2).[22,23] Chemotherapy treatment was administered every 3-4 weeks. As in the ALPI trial, thoracic RT could be given according to the preregistration policy of each center. The planned number of patients was 3300 to observe a 5% survival difference at 5 years (from 50% to 55%). The study started in 1995 and was stopped in December 2000 because of slow accrual after enrolling 1867 patients. The median follow-up was 56 months. Compliance with chemotherapy was good; 74% of patients received ≥ 240 mg/m^2 of cisplatin. Only 23% of patients on the chemotherapy arm experienced grade 4 toxicity. There was a toxic death rate of 0.8%, which was attributed to the administration of chemotherapy. Disease-free survival and OS were increased by chemotherapy, with absolute survival benefits of 5.1% (P = 0.003) and 4.1% (P = 0.03), respectively.[22] However, a comparison of the risk–benefit profile of the different regimens used in this study is clearly difficult to ascertain, as the choice of regimen was not stratified and patient case mix among centers could be extremely variable.

In the ALPI and IALT studies, relapse and recurrence of neoplastic disease accounted for the main cause of death and, more relevantly, in both arms of the ALPI study, > 40% of patients had brain relapses.

Another feature common to both trials was the suboptimal compliance with adjuvant chemotherapy, with 8% and 9% of patients who never received chemotherapy and 26%-31% of patients who received less than the 3 planned courses of treatment, which compromised the relative dose intensity. In a comparative analysis of IALT and ALPI, delivery ability of chemotherapy did not differ dramatically when a doublet combination was used instead of a triplet combination. Furthermore, the ALPI study showed that MVP conferred only a small, statistically nonsignificant, OS advantage even in the per-protocol exploratory analysis that compared outcomes among patients receiving all 3 planned cycles of chemotherapy with those of patients undergoing no adjuvant therapy.

Reasons for reduced therapeutic compliance may be related to the need for more time to fully recover from the surgical procedure itself for patients with lung cancer in comparison with the time needed for patients with breast cancer and may also be related to a negative selection bias of the patients enrolled in both studies. In the ALPI and IALT studies, 26% and 35% of patients received pneumonectomies, a percentage far exceeding the normal pneumonectomy rate in any surgical series.

Data have been recently reported about adjuvant chemotherapy in a subgroup of patients with surgically resected disease enrolled in the British Big Lung Trial. Three hundred sixty-eight patients were randomized to receive cisplatin-based doublet (38%) or triplet regimens (62%). The reported HR for OS was 1.02, but the limited sample size, quality of surgery, and limited follow-up period greatly reduce the power of the information provided.[29]

Different from ALPI and IALT, 2 additional adjuvant trials used third-generation chemotherapy regimens and were focused on a more restricted patient population. The results of the 2 trials were presented at the 40th Annual Meeting of the American Society of Clinical Oncology in 2004. Both studies were designed in the mid-1990s to compare adjuvant carboplatin/paclitaxel (Cancer and Leukemia Group B [CALGB] 9633 study)[25] or cisplatin/vinorelbine (National Cancer Institute of Canada [NCIC] BR.10 study)[26] with no adjuvant therapy for patients with completely resected stage IB disease (CALGB trial) or stage IB/II NSCLC (NCIC-BR.10; Table 3).[25,26]

The CALGB 9633 study accrued patients very slowly and, based on occurrence of events over time, the requested number of patients was amended to 384. It was well balanced for known prognostic factors between the treatment and control arms. An independent data monitoring committee stopped the study early at a planned interim analysis after the inclusion of 344 patients based on unequivocal superiority of one arm over the other.

The CALGB 9633 study demonstrates a remarkable improvement in OS compared with the no-treatment group (12% at 4 years). However, it should be known that the median follow-up is only 34 months, and there is still a huge number of censored patients on both survival curves. The magnitude of benefit of the use of adjuvant carboplatin/paclitaxel was substantially greater than one might have predicted on the basis of IALT and the metaanalysis, and, considering the available data, an overestimation of the treatment effect appears reasonable.

Table 3 Patient Characteristics and Main Efficacy Outcomes of the CALGB 9633 and NCIC BR.10 Studies[25,26]

Characteristic or Outcome	CALGB 9633[25]		NCIC BR.10[26]	
	Observation (n = 171)	Treatment* (n = 173)	Observation (n = 239)	Treatment† (n = 243)
Male Sex	63%	65%	64%	66%
PS of 0	58%	55%	49%	49%
Squamous Histology	38%	39%	38%	37%
Stage IB Disease	100%	100%	45%	46%
Stage II (A/B) Disease	0	0	55%	54%
Survival	4-Year	4-Year	5-Year	5-Year
Progression-free	50%	61%‡	48%	61%§
Overall	59%	71%‖	54%	69%¶
Median Follow-up Time	34 Months		Not available	

*Treatment consisted of carboplatin/paclitaxel.
†Treatment consisted of cisplatin/vinorelbine.
‡P = 0.035.
§P = 0.012.
‖P = 0.028.
¶P = 0.002.

Most notably, the delivery of chemotherapy was excellent in the treatment group, nearly 85% of patients in the treatment group received 4 cycles of chemotherapy. Toxicity in this group of patients was minimal, with only 36% of patients having grade 3/4 myelosuppression. There were no treatment-related deaths, which is an important aspect of an adjuvant study. Dose delays were uncommon, attesting to the well tolerated nature of the chemotherapy.[25]

It could be argued that the positive results were caused by a uniform patient population, a regimen that was well tolerated and nontoxic, and the fact that such a high fraction of patients was able to complete all the planned cycles of chemotherapy. The NCIC-BR.10 study randomized 482 patients with completely resected stage IB/II NSCLC to observation or 4 cycles of cisplatin/vinorelbine (Table 3). Cisplatin was given on days 1 and 8, which allowed for better dose intensity. Overall survival was significantly improved (5-year survival, 69% vs. 54%; HR, 0.69; P = 0.01) as well as PFS.

This regimen was less well tolerated than in the CALGB study, with the occurrence of grade 3/4 neutropenia in 73% of the patients and febrile neutropenia in 6%. Thirty-four percent of patients did not begin therapy or received only 1 cycle, and adjuvant treatment was terminated early for patient refusal in 30% of the cases and drug toxicity in 12% of patients.[26] All together, these toxicity issues partially limit the applicability of such treatment in the daily practice.

Why were these 2 studies largely positive, exceeding so far the 5% benefit hypothesized by the metaanalysis and confirmed by the IALT study? Several potential confounding factors should be taken into consideration. First, each adjuvant study enrolled a select patient population (Table 4)[22,23,25,26]; therefore, it is not known how much is representative of the entire population of patients with completely resected NSCLC. Second, in many of these studies no information is available about the proportion of patients who, during surgical resection, underwent systematic lymph nodal dissection or mediastinal lymph node sampling. In a recent randomized clinical study, systematic lymph nodal dissection was found to significantly influence survival in every stage of resectable NSCLC.[32] Third, patients with lung cancer frequently have comorbidities, including chronic obstructive pulmonary disease and cardiovascular diseases, that were found to significantly affect survival.[33,34] Additionally, an imbalance in the proportion of patients who potentially quit smoking after radical surgery may account for survival differences. This is shown in a study of 273 patients with pathologic stage I NSCLC in which the amount of smoking exposure was found to be a highly significant predictor of OS.[35]

Uracil/Tegafur–Based Trials and Metaanalysis

Several Japanese trials have evaluated the potential of oral fluorouracil derivatives as adjuvant treatments alone or in combination with other agents. Initially, 2 Japanese trials investigated the prolonged administration (6 months to 1 year) of uracil/tegafur (UFT; molar ratio of 1:4). Both trials considered eligible patients with completely resected NSCLC of stages I-III and showed a survival advantage for patients treated with UFT. In one study, patients were randomized to cisplatin, doxorubicin followed by

Table 4 Patient Enrollment of Randomized Studies of Adjuvant Chemotherapy[22,23,25,26]

Study	Enrollment Period	Enrolled Patients	Enrolled Patients per Year
IALT[22]	1995-2000	1867	339
ALPI[23]	1994-1999	1209	242
CALGB 9633[25]	1996-2003	344	49
NCIC BR.10[26]	1995-2000	482	80

UFT, or observation; whereas in the other study, patients were randomly allocated to receive 1 cycle of cisplatin/vindesine followed by oral UFT for 1 year, oral UFT alone, or observation.[36,37] In the first trial, survival advantage was shown only after adjustment in the imbalance for major prognostic factors, whereas in the second, postoperative chemotherapy was found to be a significant prognostic factor for survival. The overall 5-year survival rates were 64.1% for the UFT group (n = 103) and 49% for the surgery-alone group (n = 98; $P = 0.02$).

A clinical study limited to 225 patients with stage I/II NSCLC reported on oral UFT with MVP as adjuvant chemotherapy. The 5-year survival rates were 71.1% for the surgery-alone group and 76.8% for the chemotherapy group, with no significant difference observed. A subset analysis showed prognostic advantage for the chemotherapy group.[38] Another study randomized 221 patients with resected stage I/II NSCLC to UFT alone or control and failed to show any improvement in 5-year survival rate (79% vs. 75%).[39] At the beginning of 2004, a large confirmatory phase III trial of adjuvant UFT for 2 years versus control in resected stage I adenocarcinoma of the lung was reported. Stratification was based on age, sex, and pathologic stage (T1 vs. T2). Final results at 5 years showed a modest but significant OS benefit ($P = 0.035$) that was essentially confined to patients with T2 disease ($P = 0.051$).[40] One questionable point in this trial is the absence of any advantage in disease-free survival (DFS) for the UFT-treated arm, which clearly contrasts with all the positive platinum agent–based adjuvant studies (IALT,[22] NCIC BR.10,[25] CALGB 9633[26]) in which improvement in OS for patients receiving adjuvant chemotherapy was invariably associated with a similar or greater magnitude of improvement in DFS.

Most of the previously mentioned trials have been included in a specific metaanalysis evaluating the efficacy of UFT alone, including 2003 patients globally, 90% with stage I NSCLC. Patients treated with UFT had improvements in 5-year survival of 4.6% (HR, 0.77; 95% CI, 0.63-0.94; $P = 0.01$) and 7-year survival of 7% (HR, 0.74; 95% CI, 0.61-0.88; $P = 0.001$).[41]

In most of these UFT studies, adjuvant treatment was planned for 2 consecutive years, and treatment compliance was generally higher than that observed in cisplatin-based studies. The concept of relatively mild, low-dose continuous adjuvant therapy is attractive, but the absence of confirmatory adjuvant UFT studies outside Japan strongly limit the applicability of these data into clinical practice because, even recently, randomized studies in second-line treatment for NSCLC with gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase (TK) inhibitor, indicated a different activity of the drug when tested among Japanese and non-Japanese patients.[42,43]

Molecularly Targeted Agents in the Adjuvant Setting

There is a good rationale for the use of molecularly targeted therapies in early NSCLC, considering that many of the pathways these agents target have been shown to be altered in very early phases in the natural history of the disease.[44] The small-molecule TK inhibitor gefitinib inhibits EGFR, believed to promote tumor cell growth and metastases. A phase III randomized trial will test the effectiveness of gefitinib in the adjuvant setting for patients with curatively resected stage IB, II, or IIIA disease. The trial will compare OS for patients treated with daily gefitinib or placebo. Treatment in both arms will continue for 2 years in the absence of disease progression or unacceptable toxicity. The projected accrual is 1242 patients (621 per treatment arm), with patients stratified according to disease stage (stage IB vs. II vs. IIIA) and histologic subtype (squamous cell vs. other types). After publication of the IALT study of adjuvant cytotoxic chemotherapy, cisplatin-based therapy was considered a therapeutic option before the randomization of the patients, and it is now considered a stratification factor. The trial will also determine the prognostic significance of the EGFR expression level, phosphorylation, and mutations in the primary tumor.

Molecular Prognostic Factors

In 30% of lung adenocarcinomas and in approximately 10% of large-cell carcinomas, the K-*ras* gene was found to be mutationally activated, and in pivotal studies this feature was a prognostic determinant of survival, regardless of the stage of disease.[45] These data have not been fully confirmed by additional clinical studies.[46] The genetic alterations affecting the *p53* gene are among the most common changes that occur during malignant progression of several types of tumors, including NSCLC. However, studies that explored the prognostic role of *p53* mutations in NSCLC reported highly conflicting results and no definitive information could be obtained from those studies.[47]

The expression of K-*ras, p53*, and Ki-67 was prospectively evaluated in subgroups of patients included in the ALPI trial; unfortunately, no relevant prognostic implication was found.[23] The CALGB 8633 study also aimed at evaluating the prevalence of 10 molecular biologic markers (growth factors HER2/*neu* and K-*ras* codon 12 mutations, cell-cycle factors Ki-67 and retinoblastoma, apoptosis factors *p53* and *bcl-2*, angiogenesis factor VIII, and adhesion protein CD44, and motility factor gelsolin) to determine the influence of adjuvant chemotherapy on cancer-free survival relative to marker expression in these patients, but this information is not yet available.[30] However, it should be noted that the largest biomarker study, retrospectively performed in 515 cases of resected stage I NSCLC, failed to show any significant association between survival and the expression of an extensive panel of biomarkers, including EGFR, HER2/*neu*, *bcl-2*, *p53*, and angiogenesis.[48]

Neoadjuvant Studies in Early-Stage NSCLC

The benefits of neoadjuvant chemotherapy have already been widely accepted in the setting of locally advanced marginally resectable (stage IIIA N2) and unresectable disease (stage IIIB). A pivotal phase III study of a French thoracic cooperative group compared the administration of 2 courses of mitomycin C/ifosfamide/cisplatin followed by surgery compared with surgery alone in resectable stages I-IIIA disease. Responding patients received additional chemotherapy after surgery. The response rate to induction therapy was 64% (11% pathologic complete response). A survival advantage, potentially delayed for high perioperative toxicity, was observed in the combined arm. Median

Table 5 Ongoing Neoadjuvant Studies in Resectable Non–Small-Cell Lung Cancer

Study	Induction Treatment	Current Accrual	Planned Accrual
US Intergroup (SWOG 9900)*	Carboplatin/Paclitaxel	356	600
MRC LU22/ EORTC	Mitomycin C/Vinblastine/Cisplatin, Mitomycin C/Ifosfamide/Cisplatin, Vinorelbine/Cisplatin	450	600
ChEST	Gemcitabine/Cisplatin	250	700
NATCH	Carboplatin/Paclitaxel	400	628
IFCT (France)	Carboplatin/Paclitaxel or Gemcitabine/Cisplatin	300	520

*The study was halted in July 2004 after the presentation of the data of the CALGB 9633 and NCIC BR.10 trials showing the positive impact of adjuvant chemotherapy.[25,26]
Abbreviations: IFCT = Intergroupe Francophone de Cancérologie Thoracique; MRC = Medical Research Council

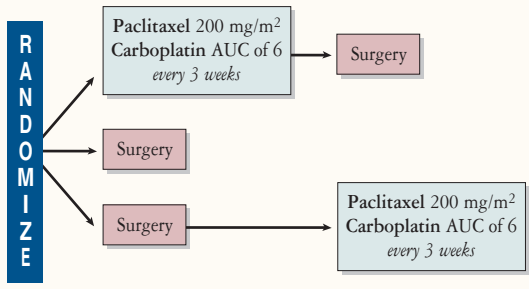
survival time favored the combined approach (36 months vs. 26 months; $P = 0.11$, log-rank test). After 150 days, the effect of perioperative chemotherapy on survival was significantly favorable (relative risk, 0.71; $P = 0.03$). A quantitative interaction between nodal stage and treatment was also noted, with the benefit from perioperative chemotherapy confined to patients with N0/1 disease ($P = 0.008$). Disease-free survival was significantly longer in the perioperative chemotherapy arm ($P = 0.02$), with a similar interaction in patients with N0/1 disease ($P = 0.002$). Risk of distant metastasis was significantly decreased in the group treated with preoperative chemotherapy (HR, 0.54; $P = 0.01$).[49]

Recently, several other neoadjuvant chemotherapy trials in the setting of resectable disease (Table 5) have been initiated. Unfortunately, the accrual of patients in these studies is slow and may further be compromised by the fact that a surgery-alone arm is considered unethical based on the results of the recently concluded adjuvant studies.

The Southwest Oncology Group (SWOG) S9900 trial was planned to assess whether preoperative chemotherapy with paclitaxel/carboplatin improves survival compared with surgery alone in previously untreated patients with stage IB, II, or selected stage IIIA (T3 N1) NSCLC. Operative mortality, response, and safety are evaluated. Samples will also be evaluated for molecular biologic factors and any correlation with outcome. Patients have been stratified on the basis of disease stage (IB/IIA vs. IIB/IIIA). The planned number of patients was set at 600, but the trial closed on July 15, 2004, because of the previously described studies showing the efficacy of adjuvant chemotherapy in this patient population, making continued accrual to the control arm inappropriate.

Similar to the SWOG 9900, the Chemotherapy in Early Stages Trial (ChEST) evaluates the role of preoperative chemotherapy in patients with resectable stage IB, II, and selected IIIA (T3 N1) NSCLC, but the chemotherapy evaluated consists of gemcitabine 1000 mg/m^2 on days 1 and 8 and cisplatin 75 mg/m^2 on day 2. Patients are randomized to immediate surgery followed by observation or induction gemcitabine/cisplatin for 3 cycles followed by surgery. Patient accrual was set at 700 and currently > 250 patients are entered in the study. The primary endpoint is OS.

Figure 1 NATCH Treatment Schema



The Neoadjuvant Taxol® Carboplatin Hope (NATCH) trial compares the benefit of preoperative versus postoperative chemotherapy with paclitaxel/carboplatin versus surgery alone in stage IA (> 2.5 cm), IB, II, and IIIA (T3 N1) NSCLC. Planned accrual was set at > 600 patients. Paclitaxel 200 mg/m^2 over 3 hours and carboplatin at an area under the curve of 6 are administered before surgery (arm 1) or after surgery (arm 3; Figure 1). Genetic polymorphisms for the xeroderma pigmentosum D gene at codons 751 and 312 were also evaluated for a correlation with response to treatment. Preliminary data about this trial are awaited in 2005.

Finally, a new French trial is currently evaluating the efficacy of 2 different regimens (cisplatin/gemcitabine and carboplatin/paclitaxel) and 2 different schedules (2 vs. 4 cycles of preoperative chemotherapy) in patients with stage I/II NSCLC. The expected number of patients is 130 in each arm for a total number of 520 patients. The primary endpoint is OS.

Conclusion

The most recent randomized studies of adjuvant chemotherapy testing the efficacy of the newer generation of cytotoxic agents in combination with platinum compounds have suggested a positive impact on efficacy outcomes (DFS and OS). A precise estimation of the survival gain that a metaanalysis estimated to be approximately 5% at 5 years needs to be fine-tuned. Two randomized clinical studies performed in highly selected patient populations support the use of adjuvant treatment in completely resected stage IB/II NSCLC. Two additional larger randomized clinical studies (one marginally positive and one marginally negative) in all stages of completely resected NSCLC indicate that, if any benefit from adjuvant chemotherapy exists, it is approximately 5% at 5 years. Another metaanalysis that will review the most recent generation of these positive and negative randomized clinical studies performed in the past 10 years will greatly contribute to assess more precisely the role of adjuvant chemotherapy.

Despite these encouraging results, reliable predictive and prognostic factors represent a priority to avoid the exposure of most patients to unnecessary treatments. In this perspective, genomics (or pharmacogenomics) and proteomics may in the near future drive the detection of those patients who are ideal candidates for adjuvant treatments. Although molecular-target-

ed therapies appear in the adjuvant setting as a rationally designed approach, clinical validation of these "proof of principle" concepts through carefully designed clinical trials is absolutely mandatory.

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