The ALPI Trial: The Italian/European Experience with Adjuvant Chemotherapy in Resectable Non–Small Lung Cancer

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Abstract Postoperative treatments for lung cancer have been evaluated for more than two decades, but in the majority of the studies no significant and clinically meaningful effect on survival has been shown. In 1995, a meta-analysis of eight cisplatin-based adjuvant chemotherapy trials in 1,394 patients with non–small cell lung cancer showed a 13% reduction in the risk of death ($P = 0.08$). The nonstatistically significant benefit reported in the meta-analysis prompted the planning of several randomized studies of platinum-based chemotherapy. Three studies addressed the issue of adjuvant chemotherapy in all the resected stages of non–small cell lung cancer (I-IIIA): the Italian/European study Adjuvant Lung Cancer Project Italy, the International Adjuvant Lung Cancer study, and the British Big Lung Trial. In contrast to the International Adjuvant Lung Cancer, the Adjuvant Lung Cancer Project Italy and the underpowered British Big Lung Trial failed to prospectively confirm a significant role of adjuvant chemotherapy in completely resected non–small cell lung cancer. In this article, we will discuss the findings of the Adjuvant Lung Cancer Project Italy study in the context of the International Adjuvant Lung Cancer and British Big Lung Trial.

Lung cancer remains the most common fatal malignancy among men and women in Europe (1) and worldwide (2). In non–small cell lung cancer (NSCLC), which represents >80% of all newly diagnosed cases of lung cancer, the main curative therapeutic approach for early disease (stage IA-IIB) is surgery. Unfortunately, these cases represent only a minority (20-25%) of all cases of NSCLC. The rationale for use of systemic therapy in completely resected NSCLC is based on follow-up studies after radical resection that have shown the predominance of distant failures over local recurrences and on clinical and pathologic evidence of early microdissemination of the disease at the time of surgery. 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 their disease within 5 years (3, 4).

Postoperative treatments, including chemotherapy, radiotherapy, or both, have been evaluated for more than two decades, and in the vast majority of the studies, no significant and clinically meaningful effect on survival has been shown. In 1995, a meta-analysis done in different subgroups of NSCLC patients receiving chemotherapy overviewed eight cisplatin-based adjuvant chemotherapy trials in 1,394 patients and found a 13% reduction in 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 postoperative cisplatin-based chemotherapy compared with patients who received only postoperative radiotherapy ($P = 0.46$). On the other hand, adjuvant chemotherapy with long-term alkylating agents was significantly detrimental (5).

These findings failed to have an effect on 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 differences in the staging modalities strongly limited the applicability of the results of this meta-analysis. However, the nonstatistically significant benefit in 5-year survival reported in the NSCLC meta-analysis generated enough enthusiasm to prompt the planning of several randomized adjuvant studies, all platinum-based chemotherapy (with or without thoracic radiotherapy), in completely resected NSCLC stages I, II, and IIIA. Most of these studies have been recently presented and published.

Among this last generation of randomized studies, only three addressed the issue of adjuvant chemotherapy in all resected stages of NSCLC (stages I-IIIA): the Italian/European study Adjuvant Lung Cancer Project Italy (ALPI; ref. 6), the International Adjuvant Lung Cancer (IALT) study (7), and the British Big Lung Trial (8). The latter was clearly underpowered to look at differences in survival in the range of the 5% indicated by the meta-analysis, whereas the other two (ALPI and IALT) were adequately sized to look at this slim difference. Unfortunately, IALT enrolled only 56% of the original sample size (against 92% of the ALPI), increasing the possibility of a type I error.

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Grant support: Associazione Italiana per la Ricerca sul Cancro and Consiglio Nazionale delle Ricerche-Applicazioni Cliniche della Ricerca Oncologica.
Presented at the International Conference on Early-Stage Lung Cancer: New Approaches to Evaluation and Treatment, October 1-2, 2004, Cambridge, Massachusetts.
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ALPI Study: Patients and Methods

In the ALPI study, 66 Italian centers were involved starting April 1995; an additional 5 European centers outside Italy and affiliated with the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group joined the study at a later time. In this study, patients who had undergone complete resection of pathologically documented stage I, II, or IIIA NSCLC were eligible. Lobectomy or pneumonectomy was strongly recommended; however, more limited resections, although pathologically completed, were allowed. The International Union Against Cancer staging system for lung cancer used at the time of the study served as a guide to stage patients. Lymph node levels were defined according to the criteria of the American Thoracic Society (9).

Surgical procedures for mediastinal staging and treatment included either a complete dissection of mediastinal lymph nodes at levels 4, 7, and 10 during right-sided thoracotomy and at levels 7 and 5 or 6 or both during left-sided thoracotomy or a systematic sampling of representative lymph nodes at the specified levels. Additional eligibility criteria included adequate bone marrow reserve (WBC count $\geq 3.5 \times 10^9$/L, platelets $\geq 120 \times 10^9$/L, hemoglobin ≥ 10 g/L, and hematocrit $\geq 30\%$), liver and renal function (creatinine <1.5 times the upper normal limits), and a postoperative FEV1 value >1.2 L.

All eligible patients were to be randomized within 42 days after surgery to receive either the MVP regimen (mitomycin 8 mg/m^2, day 1; vindesine 3 mg/m^2, days 1 and 8; and cisplatin 100 mg/m^2, day 1, every 3 weeks for three cycles) or no chemotherapy. The study design was fully reported in the original report (6). Randomization was done centrally; stratification included pathologic tumor and node descriptors according to the tumor-node-metastasis staging system, investigational center, and intended radiotherapy.

Patients who experienced progressive disease or unacceptable toxicity, or who did not receive chemotherapy for 6 weeks from the time of the last treatment, were discontinued from the study. The second and third cycles of chemotherapy were administered every 3 weeks only if patients fully recovered from the toxicities of the previous cycle of therapy; otherwise, chemotherapy was delayed 1 week, and in any persistent grade 2 toxicity, a 25% dose reduction was planned on day 28. For any higher toxicity grade, the next cycle was further delayed 1 week. Toxicity was graded according to WHO criteria (10).

Adjuvant radiotherapy was left to the policy of the participating centers and, if given, it was planned by stage at the start of the study; in the experimental arm, radiotherapy initiated 3 to 5 weeks after the last MVP treatment, and in the control arm 4 to 6 weeks after radical surgery. In both arms, total radiotherapy dose was 50 to 54 Gy (2 Gy/daily fraction, 5 days a week) over 5 to 6 weeks. Radiotherapy treatment to the clinical target volume was administered through two or three anteroposterior, posteroanterior, lateral, or oblique fields. In case of documented extracapsular invasion of any nodal station, an additional 6 Gy dose was specifically delivered. Acute and late radiotherapy toxicity was graded according to Radiation Therapy Oncology Group criteria (11).

Once patients were off the protocol therapy (chemotherapy and/or radiotherapy), they were monitored for assessment of disease status every 3 months for 2 years, every 6 months during the third year, and annually thereafter. Monitoring consisted of clinical examination as well as chest radiography done every 6 months for 2 years and once a year thereafter. Patients were flagged with the national death registry.

Statistical Plan and Analysis

The primary end point was overall survival (defined as death from any cause). Secondary end points were progression-free survival (defined as the time to the earliest recurrence or death from any cause) and toxicity of chemotherapy. The sample size was calculated to show a 20% relative reduction of mortality induced by adjuvant chemotherapy; with a 80% power and a 5% significance (two-sided) level, 535 events were required. Based on these estimates and the expected recruitment rate, it was estimated that ~1,300 patients would be needed to complete the study. The study was prematurely closed after having included 93% of the planned sample size. This decision was taken due to a lower accrual rate during the last 6 months of the trial; however, the follow-up time was prolonged to reach the originally planned number of events. A 20% relative reduction in mortality hazard ratio (HR) translates into absolute improvements in the probability of surviving 5 years of ~7% to 8% over a wide range of possible survival rates in the control group (35-55%).

The data were analyzed for overall survival in all randomized patients (including protocol violators) on an intention-to-treat basis using the log-rank test without adjustment for prognostic factors. Additional analyses were done with the Cox proportional hazards model, adjusted for baseline characteristics. A Cox model was also developed to assess the effect of the molecular prognostic factors investigated. Data monitoring and quality control procedures were set in place to ensure the quality of the information collected by the participating centers. These included random site visits and source validation procedures. An independent data monitoring committee was set up to check the progress of the trial.

Molecular Prognostic Factors Subproject

In selected centers, tumor tissue samples were centrally collected and evaluated for the presence/absence of K-*ras* mutation and for the degree of positivity to p53 and Ki-67 immunostaining. Paraffin-embedded, formalin-fixed specimens from surgically removed tumors were used to assess p53 and Ki-67 status by immunohistochemistry [Ab-2 (Oncogene Sciences, Manhasset, NY) and MIB-1 (DAKO, Glostrup, Denmark); refs. 12, 13]. Conditions for the PCR and the detection of point mutations for codon 12 K-*ras* using mutation-specific oligonucleotides were done according to procedures published previously, and the results were scored as positive or negative (14).

Results

Over a 5-year enrollment period, a total of 1,209 patients (1,086 from the Italian centers and 123 from European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group) were enrolled in the study, 606 allocated to chemotherapy and 603 to control arm. Thirteen patients were excluded from the analysis due to eligibility criteria violations (4 in MVP and 9 in the control arm). All the cases from one center (108 cases, 54 in the MVP arm and 54 in the control arm) were excluded from the final analysis because of serious concerns about data integrity. The analysis thus included 1,088 patients, 548 in the chemotherapy arm and 540 in the control arm. Patient characteristics are reported in Table 1. Data about treatment compliance indicate that 69% completed the MVP treatment, half of them with some dose adjustment or omission of the planned regimen, mainly concerning vindesine administration on day 8. In total, 22% stopped MVP treatment early, either for toxicity or for patient

Table 1. Selected patient, disease, and treatment characteristics [*n* (%) of patients]

Characteristics	MVP	Control
Male	472 (86)	465 (86)
Median age (y)	61	61
Range	33-76	37-76
Pathologic stage		
I	216 (39)	207 (38)
II	172 (31)	183 (34)
IIIA	160 (29)	150 (28)
T_1	118 (22)	100 (19)
T_2	345 (63)	360 (67)
T_3	85 (16)	80 (15)
N_0	257 (47)	254 (47)
N_1	154 (28)	151 (28)
N_2	137 (25)	135 (25)
Histology		
Squamous	278 (51)	262 (49)
Adenocarcinoma	196 (36)	206 (38)
Large cell carcinoma	27 (5)	31 (6)
Bronchoalveolar carcinoma	23 (4)	20 (4)
Others	24 (4)	21 (4)
Type of surgery, pneumonectomy	134 (24)	140 (26)
Lymph node dissection, complete	313 (57)	290 (54)
Planned radiotherapy	238 (43)	232 (43)

refusal. Chemotherapy was never started in an additional 48 (9%) patients, mainly following consent withdrawal. Regarding those patients in whom sequential radiotherapy was planned, it was completed by 65% of the patients in the MVP arm and by 82% in the control group.

Hematologic toxicity was the most common adverse effect in the MVP arm, with grade 3 and 4 neutropenia occurring in 16% and 12% of patients, respectively. During sequential radiotherapy, grade 3 and 4 hematologic toxicity were infrequent (2% in the MVP arm and 3% in the control arm), and esophagitis grade 2 to 3 was the most commonly reported adverse effect (16% in the MVP arm and 15% in the control arm). One patient in the control arm experienced grade 4 esophagitis during radiotherapy. Grade 2 to 3 acute pneumonitis was recorded in 6% in the MVP arm and 9% in the control arm, whereas grade 4 acute pneumonitis was seen in two patients in the control arm. There were 10 treatment-related deaths during the study (3 in the MVP and 7 in control arm). The most common cause of death was cancer progression, accounting for 71% of the causes of death, followed by nonneoplastic causes (16%) and by unknown causes (9%); deaths due to a second primary cancer or treatment-related cancer were documented in 11 patients (MVP = 5 and control = 6) and 10 patients (MVP = 3 and control = 7), respectively.

At the time of the final analysis, 456 (42%) patients were alive without evidence of disease and 64 (6%) were alive with recurrent disease. After a median follow-up time of 64.5 months, differences in progression-free survival (HR, 0.89; $P = 0.144$) and overall survival (HR, 0.96; $P = 0.585$) were not statistically significant. Figures 1 and 2 represent progression-free and overall survival by stage: no significant interaction between treatment and stage of disease emerged. It is remarkable to observe that in the subgroup of patients with stage II NSCLC, although the HR was not statistically significant, a 10% benefit at 5 years for chemotherapy-treated patients was reported for overall survival as well as for progression-free survival.

In the multivariate analysis for baseline and treatment characteristics, only stage of the disease and, to a lesser extent, gender emerged as independent prognostic factors (Table 2). The "per protocol" analysis to compare overall survival among patients receiving all the planned three cycles of chemotherapy with that of patients who underwent no adjuvant therapy showed no statistically significant difference between the two groups (HR, 0.86; 95% confidence interval, 0.71-1.04).

In the molecular prognostic factors substudy, 38% of the primary tumors were analyzed for p53 and Ki-67 expression; 50% and 62% of tumor specimens were positive for p53 and Ki-67, respectively, in >25% of examined cells. No correlation with stage, histology, and p53 or Ki-67 expression was found even when several cutoff points were considered for positivity. K-*ras* mutation analysis was assessed only in adenocarcinoma and large cell carcinoma specimens because a preliminary analysis done in the first 50 cases of squamous cell carcinoma revealed the presence of a point mutation in only 2% of tumor samples. In all, 117 cases were analyzed, and an additional 23 cases were not successfully amplified. Point mutations at exon 1 were detected in 22% of the cases.

Discussion

The ALPI trial was the first large, prospective adjuvant study designed to detect reasonably small differences in survival and in the range of those reported by the NSCLC meta-analysis. In addition, it was the first large-scale adjuvant trial in lung cancer that successfully enrolled several patients very close to that originally planned. Subsequently, IALT, another large randomized study, aimed to determine the effect on overall survival of a chemotherapy regimen that included cisplatin (80-120 mg/m^2) and either a *Vinca* alkaloid (vindesine 3 mg/m^2/wk, vinblastine

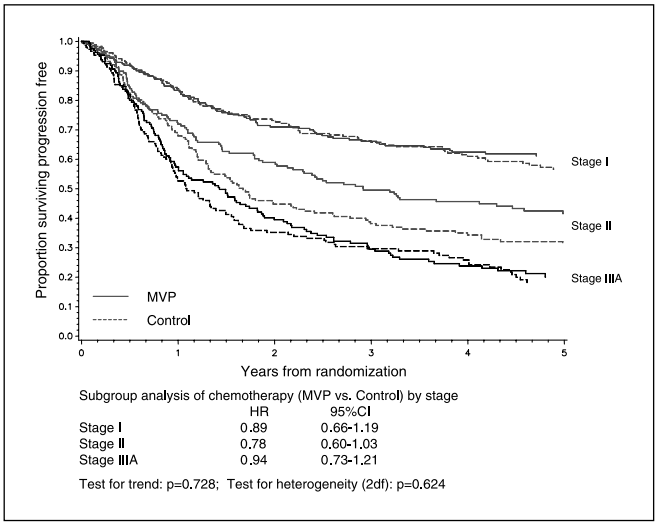

Fig. 1. Progression-free survival by stage.

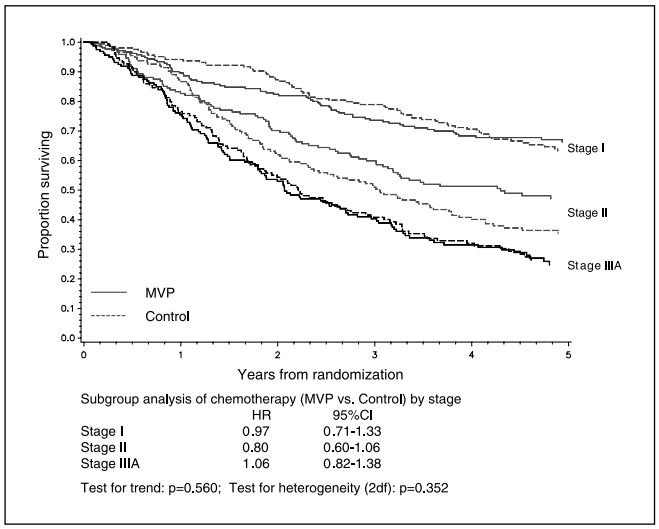

Fig. 2. Overall survival by stage.

4 mg/m^2/wk, or vinorelbine 30 mg/m^2/wk) or etoposide (100 mg/m^2/d, 3 consecutive days) compared with no chemotherapy after complete surgical resection in patients with stage I, II, or III NSCLC. This trial showed a statistically significant effect of adjuvant chemotherapy on disease-free and overall survival rates with an absolute survival benefit at 5 years of 5.1% (P = 0.003) and 4.1% (P = 0.03), respectively (7). The planned number of patients was 3,300 to observe a 5% survival difference at 5 years (50-55%). The study started in 1995, and in December 2000, after enrollment of 1,867 patients, the study was closed due to slow accrual. The median follow-up was 56 months. Compliance with chemotherapy was good: 74% of patients received at least 240 mg/m^2 cisplatin. Only 23% of patients on the chemotherapy arm experienced grade 4 toxicity.

In clinical trials in which a long follow-up is undertaken, the difference between treatments may depend on the follow-up time. That implies that in the early phase of the study there is the potential for a biased estimate of the treatment effect. In the IALT study, the accrual was prematurely interrupted when <60% of expected patients had been enrolled. The follow-up continued until ~65% of expected events had been observed. If the study was continued until the planned number of events was reached, the conditional power to detect, under the null hypothesis, a statistically significant difference would have been <50%. Moreover, the adoption of a Bayesian approach, which may be appropriate for interpreting results when anticipated analysis seems to be indicating a positive treatment effect, would have suggested prolonging the follow-up.

In both ALPI and IALT, relapse and recurrence of the neoplastic disease accounted for the main cause of death; more relevantly, in both arms of the ALPI study, >40% of patients had brain relapses. Another common feature to both trials was the suboptimal compliance to adjuvant chemotherapy, with 8% to 9% of patients never starting chemotherapy and 26% to 31% of patients receiving less than the three planned courses of treatment, which compromised the relative dose intensity. In a comparative analysis of IALT and ALPI, the ability to delivery chemotherapy did not differ dramatically when a doublet combination was used instead of a triplet combination. Poor therapeutic compliance may be related to the longer postoperative recovery period needed by lung cancer patients compared with breast cancer patients, and, secondly, to a negative selection bias 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 regarding adjuvant chemotherapy in a subgroup of surgically resected patients enrolled in the large British Big Lung Trial have been recently reported. In this trial, 368 patients were randomized to receive cisplatin-based doublets (38%) or triplets (62%): the reported HR for overall survival was 1.02, but the limited sample size, the quality of surgery, and the limited follow-up period greatly reduce the power of the information provided (8). The results of another large platinum-based adjuvant trial are still awaited. In the Adjuvant Navelbine

Table 2. Multivariate analysis for clinical and molecular prognostic factors (adjusted by stage)

	Overall survival HR (95% confidence interval)	*P*	Progression-free survival HR (95% confidence interval)	*P*
Clinical variables				
Age (5-y interval)	1.06 (1.00-1.12)	0.062	1.04 (0.99-1.10)	0.149
Stage				
II vs I	2.01 (1.62-2.49)	0.0001	1.88 (1.54-2.30)	0.0001
III vs I	3.19 (2.59-3.93)		2.94 (2.39-3.53)	
Histology				
Squamous vs other	0.87 (0.73-1.03)	0.112	0.84 (0.72-0.99)	0.037
Gender				
Male vs female	1.33 (1.02-1.72)	0.034	1.19 (0.94-1.51)	0.150
Complete dissection vs sampling	0.88 (0.75-1.04)	0.135	0.86 (0.74-1.01)	0.068
MVP vs control	0.95 (0.81-1.12)	0.559	0.88 (0.76-1.03)	0.115
Molecular variables				
p53 (n = 387)	1.03 (0.98-1.08)	0.30	1.02 (0.97-1.06)	0.49
Ki-67 (n = 395)	1.42 (0.82-2.47)	0.63	1.04 (0.98-1.11)	0.16
K-*ras* (n = 108)	1.02 (0.95-1.08)	0.20	1.25 (0.73-2.14)	0.41

International Trial Association study, patients with completely resected NSCLC were randomized to chemotherapy, which consisted of four cycles of cisplatin at 100 mg/m^2 every 4 weeks and 16 cycles of vinorelbine at 30 mg/m^2/wk or observation only. In this study, 831 patients were included between October 1994 and December 2000. Data are to be reported in early 2005.

More recently, the results of two randomized studies conducted in selected patient populations with resected NSCLC (Cancer and Leukemia Group B and NCIC-JBR.10 trials) were reported for the first time. Both studies were designed in the mid-1990s to compare adjuvant carboplatin/paclitaxel (Cancer and Leukemia Group B 9633 study; ref. 14) or cisplatin/vinorelbine (NCIC-JBR.10 study; ref. 15) with no adjuvant therapy for patients with completely resected stage IB (Cancer and Leukemia Group B trial) or completely resected stage IB or II disease (NCIC-JBR.10) NSCLC. Cancer and Leukemia Group B 9633 showed a remarkable improvement in overall survival in the adjuvant chemotherapy arm compared with the no-treatment group (12% at 4 years; ref. 14). The magnitude of benefit of the use of adjuvant carboplatin/paclitaxel was substantially greater than one might have predicted based on IALT and the meta-analysis, and considering the available data, an overestimation of the treatment effect seems possible. Most notably, the delivery of chemotherapy was excellent and nearly 85% of patients in the treatment group received four cycles or more of chemotherapy (14). It could be argued that the positive results were due to a uniform patient population, a regimen that was well tolerated and nontoxic, and the fact that such a high fraction of patients were able to get all four cycles of therapy. However, it should be remembered that the median follow-up time is only 34 months, and on both survival curves, there is still a large number of censored patients.

NCIC-JBR.10 study randomized 482 patients with completely resected stage IB or II NSCLC either to observation or to four cycles of cisplatin/vinorelbine. The cisplatin was given on days 1 and 8, which allowed for better dose intensity. Overall survival was significantly prolonged in the treatment arm (94 versus 73 months; $P = 0.011$), as was recurrence-free survival (not reached versus 46.7 months; $P = 0.0003$) and 5-year survival (69% versus 54%). In contrast to the Cancer and Leukemia Group B study, this regimen was less well tolerated with no deaths due to toxicity but with grade 3 to 4 neutropenia in 73% and febrile neutropenia in 6% of patients. Compliance was lower: 34% of the patients did not start or received only one cycle of chemotherapy; among reasons for going off treatment, patient refusal accounted for 30% and drug toxicity for 12% of the cases (16). These toxicity and compliance issues partially limit the applicability of such treatment in the daily practice.

Why were these two studies largely positive, exceeding the 5% benefit hypothesized by the meta-analysis and confirmed by the IALT study? Several potential confounding factors should be taken into consideration. Firstly, all these adjuvant studies enrolled a highly selected patient population that may not be representative of the general population of completely resected NSCLC patients. Secondly, in many of these studies, no information is available about the proportion of patients who during surgical resection underwent systematic nodal dissection or mediastinal lymph node sampling. In a recent randomized clinical study, systematic nodal dissection was found to significantly influence survival in every stage of resectable NSCLC (17). Thirdly, lung cancer patients frequently suffer from comorbidities, including chronic obstructive pulmonary disease and cardiovascular diseases, which were found to significantly affect survival (18, 19). Additionally, an imbalance in the proportion of patients who quit smoking after radical surgery may potentially account for survival differences as shown in a study of 273 pathologic stage I NSCLC patients where the amount of smoking exposure was found to be a highly significant predictor of overall survival (20).

Taking into account the meta-analysis data, the nonpositive outcome of the ALPI study, and the marginally positive results reported by IALT study, coupled with the two largely positive adjuvant studies recently presented, how can we move forward? A new meta-analysis that will consider the results of all these recently presented studies would undoubtedly be the next step: this task, already planned, will need to carefully consider all, or at least most, of the potential confounding factors that may jeopardize the assessment of the biological effect of adjuvant chemotherapy in completely resected NSCLC.

Open Discussion

Dr. Thomas Lynch: Dr. Wood, thoughts from your discussion at ASCO regarding the ALPI trial? In the light now of some newer data, what is your view of adjuvant chemotherapy?

Dr. Douglas Wood: I think that the ALPI data, while they were the best at the time it was reported, have been somewhat trumped by new information from additional trials. The data from the IALT study dramatically changed the tone of the discussion from one of "does it have value" to "it works, but in which patient populations?" It's now an effort to try to optimize chemotherapy's value rather than to say it doesn't have value.

Dr. Bruce Johnson: I think the data are more consistent than disparate, in that all these data are pretty consistent in identifying the subsets of patients for whom adjuvant chemotherapy works. It appears that adjuvant chemotherapy doesn't help patients with very early stage I disease. It may help squamous cell carcinomas less than adenomacarcinomas, but that is speculation: there are no data. It becomes complicated, as was shown in the ECOG trial, when you try to do adjuvant therapy for node-positive patients. It is harder to interpret those data.

Dr. Jeffrey Bogart: You implicated radiotherapy in not seeing a benefit in certain populations in ALPI. Did you do a multivariate analysis, looking at radiotherapy as actually detrimental to those patients?

Dr. Scagliotti: We did, and at least in the multivariate analysis, radiotherapy was not detrimental. When you are looking at the IALT and ALPI trials, which are the only trials that looked at the whole population of completely resected patients, one clear difference is that more patients received adjuvant radiotherapy in the ALPI than in the IALT. I am trying just to offer an explanation as to why one study was negative and the other one was positive.

Dr. Bogart: If you look at the analysis from all patients who had planned radiotherapy, they had actually a greater chemotherapy benefit than patients who did not have planned radiotherapy. I don't think it's a valid assumption that there is a negative effect of radiotherapy. I think it's a valid observation.

Dr. Lynch: But, you know, we oncologists always blame the radiation. No matter what the circumstance is, we find a way to blame the radiation.

Dr. Bogart: We are supposed to clear that up at this conference.

Dr. Nick Thatcher: Why are we actually excluding stage IIIA patients in most of these studies?

Dr. Scagliotti: It is always complicated to reach agreement on what is radically resected from the oncologist's viewpoint and what is radically resected according to the thoracic surgeon. With stage IB and II, when you are dealing with pathologic TNM staging, you are more certain of having a homogenous population.

Dr. Lynch: Question for Dr. Shaw: we saw the data that Dr. Scagliotti presented, suggesting K-*ras* predicted inferior outcome. Do you think there will come a time when we define disease by its molecular profile as opposed to thinking more narrowly in terms of adenocarcinoma versus squamous versus small cell?

Dr. Alice Shaw: Yes, right now we're discussing three markers, p53, K-*ras*, and Ki-67, but in the future, we envision what has been called personalized molecular medicine where you actually look at a number of different genetic alterations (or even genetic polymorphisms) that contribute, for example, to a patient's tumor's sensitivity or lack of sensitivity to radiation or certain chemotherapies.

Dr. Scagliotti: It is relatively easy to talk around a table among an audience of 50 investigators, but there is not an easy way to do these kinds of studies because you need money and you need to convince pathologists to give you the tissue samples.

Dr. David Gandara: There is an interesting paradigm that is emerging regarding tobacco-related lung cancer and lung cancers that occurs in never smokers. The K-*ras* mutation and the EGFR mutations, in most people's work, are largely mutually exclusive. In other words, they do not occur together. When we've analyzed our SWOG database, we've found two patients who have EGFR mutations, who also have K-*ras* mutations. The interesting thing is, they are unusual K-*ras* mutations. They are not the ones that are highly associated with tobacco carcinogenesis.

Dr. Lynch: But if you look at the fact that K-*ras* mutations are 30%, EGFR mutations is 13%, odds alone are going to say there is not going to be that many, there might be 2%, 3%, 4% that are going to have them both. It may just be a statistical aberration as opposed to a biologic aberration.

Dr. Tyler Jacks: There are plenty of examples of nonmeaningful patterns in molecular genetics of cancer, where one does see segregation of mutations based on larger groups. The pathways are clearly related and may in the end activate the same downstream target, and we'll be able to piece it out. We are building a comparable mouse model with the same EGFR mutations, so we'll be able to do a side-by-side comparison with the K-*ras* model and compare biologies, adding the two mutations together to see if it makes any difference in the cells.

Dr. Johnson: There are two articles of over 1,000 patients that say there is no overlap between K-*ras* and EGFR mutations in patient tumors (21, 22). There will almost certainly be some, especially in special populations, but it certainly is not common.

Dr. Scagliotti: Our biological studies were done 7 years ago, at the time of surgery. So, we did the analysis in a 6-month period after surgery completely blinded for any survival data. The value of prospective studies are much higher than any retrospective study.

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Clin Cancer Res 2005;11:5011s-5016s.