Adjuvant Chemotherapy for Non-small Cell Lung Cancer

Emilio Bria, MD, Federica Cuppone, MD, Fabiana Letizia Cecere, MD, Michele Milella, MD, Cecilia Nisticò, MD, Francesco Cognetti, MD, and Edmondo Terzoli, MD

Abstract: Cisplatin must be considered the treatment standard for lung cancer chemotherapy, whatever the disease setting, at least in the Western world. After the seminal meta-analysis published in 1995, 12 randomized clinical trials (RCTs) exploring the benefits of adjuvant cisplatin-based chemotherapy have been completed, published, or presented. Although all these RCTs differ in patient features, two common suggestions emerge when the stage is taken into account: a significant benefit for chemotherapy is demonstrated for stage II and IIIA patients and none of these trials showed any significant benefit for adjuvant chemotherapy in stage IB patients. Ten years after this meta-analysis, a further individual patient data-pooled analysis exploring the eventual benefits of adjuvant cisplatin-based chemotherapy after surgery for early stage non-small cell lung cancer in the more recent RCTs has been presented. The 5-year overall survival benefit in favor of cisplatin-based chemotherapy was 5.3% (48.8% versus 43.3%, $p = 0.004$), with a relative risk reduction of 11%. These results confirm those reported by previous meta-analyses performed according to a literature-based approach. Advances are emerging in the selection of those patients who are likely to benefit more from such treatment. In this respect, the customized therapy based on molecular/genetic patient and disease features constitutes a new avenue to pursue.

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Lung cancer is the leading cancer death cause in men in the United States.[1,2] Almost 80% of all lung cancers are defined as non-small cell lung cancer (NSCLC).[2,3] Despite the recent advances in both screening and imaging tools, NSCLC is still diagnosed at local or more often distant advanced stage, whereas relatively few tumors (approximately 30%) are present at an early stage.[3] Surgery has to be considered the standard of treatment for early-stage disease, although many stage II and III patients will progress within few months after tumor resection.[3] Given the high incidence and mortality, this disease is considered a social illness in the Western countries, and for this reason, several screening programs have been established with the intent to resect as many patients as possible at earlier stages. Despite the concern over the interpretation of such randomized clinical trials (RCTs), advances in this field have been made recently.[4] In the past 15 years, large RCTs have been conducted to see whether adjuvant radiotherapy, chemotherapy, or both are able to improve local control and survival after surgery, with conflicting results. Two large meta-analyses have shed light on the existing literature of the 1990s by ruling out any supposed survival advantage for adjuvant radiotherapy (alongside specific techniques, doses, and tools) and conferring a slightly better survival trend for patients receiving adjuvant chemotherapy, although not statistically significant ($p = 0.08$).[5,6] Actually, improved locoregional control for patients receiving adjuvant radiotherapy was documented in that meta-analysis accruing more than 2000 patients.[5] These data suggested that death from lung cancer could be attributed to distant, extrathoracic metastases and that chemotherapy would work in adjuvant setting as demonstrated for advanced disease in at least two meta-analyses.[6,7] While in the advanced setting, the benefit of chemotherapy is to date well established regardless of other important prognostic factors such as performance status, its blind application for whatever stage resected NSCLC patients is still under debate. The positive trend that emerged in the Lung Cancer Collaborative Group (LCCG) meta-analysis in this merged population allowed the start of further adjuvant RCTs specifically designed to detect the observed benefits of the previous meta-analysis,[6] in some cases in a larger patient cohort.[8–11]

RCTs EXPLORING ADJUVANT CHEMOTHERAPY

The LCCG clearly established that (1) in advanced disease, cisplatin-based chemotherapy significantly improved survival versus supportive care ($p < 0.0001$); (2) cisplatin-based chemotherapy significantly improved outcome when associated with exclusive radiotherapy for locally advanced disease ($p = 0.005$); (3) a strong trend in favor of adjuvant cisplatin-based chemotherapy after surgery was documented ($p = 0.08$), whereas a significant detrimental negative effect against long-term adjuvant alkylating agents was present ($p = 0.005$).[6] Because of this evidence, cisplatin has become the treatment standard for NSCLC chemotherapy in both clinical research and daily practice, at least in the Western countries.

After the LCCG meta-analysis, 12 RCTs exploring the benefit of adjuvant cisplatin-based chemotherapy have been completed, published, or presented[6,8–19]; one of the earliest

Department of Medical Oncology, Regina Elena National Cancer Institute, Rome, Italy.
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Address for correspondence: Emilio Bria, Department of Medical Oncology, Regina Elena National Cancer Institute, Via Elio Chianesi 53, 00144, Rome, Italy. E-mail: emiliobria@yahoo.it

TABLE 1. Adjuvant Randomized Clinical Trial Characteristics

Author	No. of Pts.	Pneumonectomy (%)	Stage I/II/III (%)	RT (%)
Arriagada et al.[8]	1867	35	37/24/39	30
Scagliotti et al.[9]	1209	25	39/33/28	43
Winton et al.[18]	482	23	45/55/—	—
Waller et al.[17]	381	—	27/38/34	14
Douillard et al.[11]	840	37	35/30/35	25
Strauss et al.[15a]	344	10	—/100/—	—

a Only in abstract form. pts., patients; RT, radiotherapy.

(which started accrual before the Post-Operative Radio-Therapy meta-analysis came out) randomized stage II to III NSCLC patients to radiotherapy after surgery versus radiotherapy plus chemotherapy after surgery.[10] Only one of these RCTs has not yet been published.[15] With a median follow-up ranging from 44 to 91 months, six RCTs demonstrated a significant survival benefit for patients receiving chemotherapy.[8,11,12,14,18,19] If we consider only those RCTs with an almost adequate patient sample, the International Adjuvant Lung Cancer Trial (IALT) provided the first substantial evidence that adjuvant cisplatin-based chemotherapy would be beneficial for patients who had undergone surgery for stage I to III NSCLC.[8]

Although the previous Adjuvant Lung Cancer Project Italy/European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group trial showed no significant benefits for the experimental arm, in that study, survival for stage II patients receiving chemotherapy was shown to be better than that for those without treatment.[9] The most important contribution to this topic was provided by six RCTs, whose characteristics are listed in Table 1; different patient characteristics are present across all RCTs, in particular in staging, pneumonectomy, and radiotherapy rate.

In all these trials, cisplatin was the lead drug, with the exception of the Cancer and Leukemia Group B (CALGB) 9633 protocol, which included the carboplatin-paclitaxel doublet.[15] This trial was started after 1996, at a time when there was not so much evidence to suggest that this combination was equally efficient for cisplatin-based doublets.[20,21] The earliest presentation of the CALGB 9633 trial provided a significant survival benefit for the chemotherapy arm, but a later update demonstrated no significant differences between the two arms.[15]

Despite the differences of all these RCTs in patient features, two common considerations emerge when the stage is taken into account: (1) none of the trials showed any significant benefit for adjuvant chemotherapy in stage IB patients[8,9,11,15,18] and (2) a significant benefit of chemotherapy is demonstrated for stage II[9,11,18] and IIIA[8,11] patients.

META-ANALYSES EXPLORING ADJUVANT CHEMOTHERAPY FOR NSCLC

The first results of the Lung Adjuvant Cisplatin Evaluation (LACE) pooled analysis exploring the eventual benefit of adjuvant cisplatin-based chemotherapy after surgery for early-stage NSCLC were presented at the last American Society of Clinical Oncology (ASCO) meeting.[22] This was the first individual patient data meta-analysis after the seminal LCCG meta-analysis, which actually changed the treatment guidelines for NSCLC after 1995[6]; therefore, these updated results have been awaited worldwide from more than 10 years. The authors chose 300 patients per trial as cutoff for entry into the analysis, so they correctly called it a pooled analysis instead of meta-analysis. Although 300 patients per trial are unlikely to be sufficient to determine significant survival advantage in adjuvant NSCLC, it allowed those trials that were certainly underpowered to be ruled out. Indeed, a meta-analysis should comprehensively include all RCTs specifically designed to answer the question that the analysis is requested to explore.[23] Although apparently it seems formal, this is a fundamental issue when considering the increasing number of published and presented meta- and pooled analyses. With regard to the strict criteria according to which a high-quality meta-analysis should be designed, the LACE authors did not choose the chemotherapy benefit as the main endpoint, but the "identification of trials or patient characteristics associated with the benefit of adjuvant cisplatin-based chemotherapy for NSCLC."[22] Five RCTs with 4584 patients were included,[8,9,11,17,18] and the 5-year overall survival benefit in favor of cisplatin-based chemotherapy was 5.3% (48.8% versus 43.3%), with a relative risk reduction of 11% (hazard ratio = 0.89, 95% confidence interval: 0.82–0.96, $p = 0.004$), with no significant heterogeneity ($p = 0.34$) (Table 2). The characteristics of RCTs and patients that seemed to be associated with the benefit of chemotherapy were age, sex, performance status, type of surgery, histology, stage, drug administered with cisplatin, radiotherapy and overall cisplatin dose. Unfortunately, only few of these results have been presented in detail. Although subgroup analysis can be dangerous and easily misunderstood, given the pr-specified intent provided by the authors when the analysis started, the risk seems to have been avoided in this case.[24] The combination of cisplatin and vinorelbine seemed to be the most active among all the adopted schedules. Actually, these results may have been biased by the fact that this is the most studied combination (1888 patients), and, above all, the

TABLE 2. LACE Meta-analysis Results[22]

Subgroup	No. of Patients	HR (95% CI)
OS		
Overall analysis	4584	0.89 (0.82–0.96)
CDDP + vinorelbine	1888	0.80 (0.70–0.91)
Stage IA	347	1.41 (0.96–2.09)
Stage IB	1371	0.92 (0.78–1.10)
Stage II	1616	0.83 (0.73–0.95)
Stage III	1247	0.83 (0.73–0.95)
DFS		
Overall analysis	4584	0.84 (0.78–0.90)

HR, hazard ratio; CI, confidence intervals; OS, overall survival; CDDP, cisplatin; DFS, disease-free survival.

TABLE 3. Overview of All Meta-analyses Exploring Adjuvant Chemotherapy

Meta-Analysis	No. of Patients	HR (95% CI)
LCCG[6]	1394	0.87 (0.74–1.02)
Pignon et al.[22]	4584	0.89 (0.82–0.96)
Hotta et al.[27]	3786	0.89 (0.81–0.97)
Sedrakyan et al.[28]	3518	0.89 (0.82–0.96)
Berghmans et al.[29]	4602	0.83 (0.80–0.92)
Bria et al.[30]	7334	0.93 (0.88–0.97)

HR, hazard ratio; CI, confidence intervals; LCCG, Lung Cancer Collaborative Group.

TABLE 4. Difference between Planned and Obtained Survival Benefit across RCTs

Author	Required Sample Size	Planned No. of Courses/ Compliance	OS % Gain	
			Planned	Obtained
Arriagada et al.[8][a]	3300	3–4/74%	5% (5 yr)	4% (5 yr)
Scagliotti et al.[9]	1300	3/69%	7% (5 yr)	3% (5 yr)
Winton et al.[18]	450	3–4/65%	10% (3 yr)	15% (3 yr)
Waller et al.[17]	4000	3/64%	5% (5 yr)	0 (1 yr)
Douillard et al.[11]	800	4/76%	10% (2 yr)	5.1% (2 yr)
Strauss et al.[15][b]	384	4/85%	NR	12% (4 yr)

[a] Change in trial design.
[b] Only in abstract form.
Pts., patients; OS, overall survival; NR, not reported.

cisplatin dose combined with vinorelbine is significantly higher than with other drugs. From this perspective, we are unable to understand whether the benefit is due to vinorelbine, to the higher cisplatin dose, or both, also taking into account that this should be considered a post hoc analysis. In advanced disease, the cisplatin dose (and dose intensity) seems to play an important role in improving outcome.[25] The stage analysis confirms the data coming from both RCTs and a previous meta-analysis, i.e., chemotherapy significantly works in stages II and III, with no impact on stage IB (Table 2).[26] In particular, the best approach for stage IB patients is an intriguing issue. The update of the CALGB 9633 released at the last ASCO annual meeting did not confirm the positive survival improvement in favor of the adjuvant carboplatin-paclitaxel arm as documented at the ASCO presentation in 2004.[15] Moreover, although a significant advantage in disease-free survival in favor of chemotherapy was confirmed at the last follow-up, the interpretation of this endpoint in this setting, and actually in this disease, is not yet clear. The LACE authors concluded that (1) cisplatin-based adjuvant chemotherapy significantly improves overall and disease-free survival in patients who have undergone surgery for NSCLC; (2) the most active combination seems to be cisplatin (at the total dose of $320-400$ mg/m^2) plus vinorelbine); (3) adjuvant chemotherapy certainly provides benefit for stage II and III patients, and this benefit is independent of other prognostic factors. Although the multivariate analysis was not able to distinguish between the independent role of the cisplatin dose and the associated drug, the overall conclusions are not that different from those reported by four other literature-based meta-analyses that were published recently, as shown in Table 3.[27–30] As shared worldwide, according to the National Cancer Institute recommendation, levels for data transfer from clinical research to clinical practice, quality- and methodology-controlled meta-analyses (together with large RCTs) provide strong evidence.[31] Although individual patient data meta-analyses are considered the favorite way of collecting and summarizing the results of RCTs, the above-mentioned literature-based meta-analyses produced a homogeneous benefit in favor of adjuvant chemotherapy, with an absolute benefit ranging from 2% to 4.5%, whichever population was explored (Table 3). Even considering the subgroup analyses (although taking into account all the limitations and risks of this approach[24]), the literature-based meta-analyses demonstrated almost the very same results as the LACE.[26]

INTERPRETATION OF CLINICAL RESEARCH DATA

When trying to interpret these RCTs, many issues are still open that concern (1) applied methodology of each single trial; (2) subgroup analyses; (3) drugs used, doses, and dose intensities; (4) accrual rate and time frame; (5) overall treatment duration; (6) adjunct radiotherapy. Many of the RCTs underwent protocol revisions of the expected hazard ratios (and patient sample size) during enrollment (Table 4), and this can be considered a bias. Furthermore, the randomized patients per year/enrollment time ratio was too low in some trials, rendering the daily clinical reproducibility too far from clinical practice. Indeed, one of the largest trials that yielded a benefit with cisplatin-vinorelbine in stage II and IIIA patients had a relevant slow recruitment bias.[11] Moreover, it appears that the benefit of adjuvant chemotherapy tends to be small (approximately 2%–4%), whatever the patient sample and regimen. Although this translates into thousands of saved lives, given the social impact of this disease, treatment costs and toxicities (including toxic deaths) should be taken into account. Therefore, methodological issues and compliance with chemotherapy need to be carefully weighted when trying to interpret these RCTs (Table 2). If the positive survival results provided by the single RCTs are confirmed by the forthcoming individual patient data meta-analysis update, we should conclude that chemotherapy has an impact on the natural history of NSCLC. Actually, we are unable to understand to what extent the greater benefit coming from some specific stage and trial has contributed to the general result. Even if the data coming from subgroup analyses of the RCTs[8,11] have been confirmed by the LACE meta-analysis[22] (i.e., stage II–III, performance status $0-1$), we are still debating whether any conclusion is widely applicable or is just a hypothesis-generating exercise.[24,32] It is certain that the paradigm in the treatment of early-stage NSCLC has shifted in the past 3 years; the positive results of RCTs accruing more than 7000 patients and the meta-analyses performed offered promising results in favor of adjuvant chemotherapy. Advances are emerging about the selection of those patients who are likely to better benefit from such treatment. From another point of view, when looking at the adjuvant scenario in other tumors, an absolute increase of 4% to 8% in 5-year survival provided by chemotherapy in breast or colon cancer has been

considered worldwide sufficient to transfer the treatment into daily clinical practice. In a disease such as NSCLC, an absolute survival benefit of 2% to 4% at 5 years should be the best realistic goal, as suggested 10 years ago by the LCCG meta-analysis and confirmed by the more recent RCTs and meta-analyses.[8,11,22,27–30]

FUTURE PERSPECTIVES: CUSTOMIZED CHEMOTHERAPY

The role of customized therapy in adjuvant setting is now even more appealing than a few years ago. In particular, a number of studies have proved the relevance of predicting outcome of several genes involved in chemotherapy-induced DNA damage. Indeed, given that worldwide, and especially in European countries, cisplatin-based chemotherapy remains the gold standard in the treatment of NSCLC, several more new data have been published recently about the correlation of specific DNA repair gene expression and survival benefit of cisplatin-based chemotherapy. The NER system is the major mechanism of repair of DNA adducts induced by cisplatin[33]; this is constituted by a series of proteins, of which ERCC1 is suggested as a surrogate marker of the entire system. Several studies have analyzed the expression (measured as quantitative expression by real-time PCR [RT-PCR]) of ERCC1 in the metastatic setting of patients affected by esophageal, gastric, and pulmonary cancer.[34–36] In these retrospective studies, ERCC1 has demonstrated a predictive role in the benefit of a cisplatin-based chemotherapy in terms of response and/or survival. Very recently, the French group that conducted the IALT study published the results of the analysis of ERCC1 expression (by immunohistochemistry) and its correlation with outcome in approximately 40% of patients treated with cisplatin-based chemotherapy.[37] This retrospective analysis was able to demonstrate a significant statistical impact of no ERCC1 expression and better survival as proven by a 35% reduction in the risk of death in the group of patients who received adjuvant chemotherapy (versus those who did not). Based on the seminal results of the predictive role of ERCC1, a prospective study in metastatic NSCLC was conducted by the Spanish Lung Cancer Group and presented at the European Society for Medical Oncology meeting. Patients were randomized to standard chemotherapy or customized chemotherapy based on ERCC1 expression levels. Patients receiving customized treatment had a significantly better response. For the first time in the adjuvant setting and in a large group of patients, these findings shed light on NSCLC treatment. Pharmacogenomics could help clinicians in decision making. In fact, the use of adjuvant chemotherapy has not been established for all stages or for all patients. Moreover, bio-IALT suggests a possible large-scale application of this method by using immunohistochemistry. This could mean fast confirmation in a prospective study and easier training. These results should encourage us to improve research in this field, but they also act as a caveat: when we are facing potential markers, we need to globalize/universalize the method and render it reproducible. If not, it is advisable to leave its use to skilled researchers. Because all previous studies have retrospectively analyzed the role of

ERCC1 by RT-PCR, is important to define the role of both methods described so far. RT-PCR is more capable of defining the scale, more than a black or white expression. This could imply the introduction of different chemotherapy agents, including the newest ones.

CONCLUSIONS

More than 10 years after the publication of the seminal LCCG meta-analysis that first defined the treatment guidelines to be adopted for patients with NSCLC, we now have sufficient evidence from both RCTs and meta-analyses to recommend adjuvant cisplatin-based chemotherapy for stage II to III patients. This treatment suggestion should be clearly discussed with the patients, taking both toxicities and costs into account. More RCTs specifically addressed for stage IB and elderly patients are needed. The relatively small absolute benefits (together with the high toxicity) strongly suggest selecting patients based on findings that are different from the clinical factors. In this respect, the customized therapy based on molecular/genetic patient and disease features constitutes a new avenue to pursue.

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