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Multimodality approach to early-stage non-small cell lung cancer

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Adjuvant chemotherapy;
Pharmacogenomics;
Patient selection;
Gene expression analysis

Summary The results of large randomised studies have clearly demonstrated that adjuvant chemotherapy prolongs overall survival by approximately 5% at 5 years in patients with early-stage non-small cell lung cancer (NSCLC). The benefit appears to be largely confined to patients with stage II/III disease, although approximately 25% of patients with stage I disease are at high risk of relapse within 5 years of surgery and therefore could benefit from adjuvant chemotherapy. There is an urgent need to predict more accurately which patients are likely to relapse after surgery and who, therefore, might benefit from further therapy. Preliminary studies indicate that molecular tumour markers may be able to identify tumours that are more likely to respond to chemotherapy and patients who are more likely to achieve improved survival from those who do not benefit at all from adjuvant chemotherapy. A pivotal study has shown that analysis of tumour gene expression can be used to predict the risk of relapse with greater accuracy than that which is achievable using clinical factors. In the future, pharmacogenomics may be used in this approach to identify patients for adjuvant chemotherapy, thus increasing the efficacy of treatment and reducing the burden of therapy in patients who are unlikely to benefit from further therapy.

Contents

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1. The role of adjuvant chemotherapy in NSCLC

Following the results of a meta-analysis published 15 years ago, which showed a 5-year survival benefit of approximately 5% for adjuvant chemotherapy in patients with non-small cell lung cancer (NSCLC) [1], various large multicentre studies have investigated the benefit of adjuvant chemotherapy in this disease.

The findings of the above mentioned meta-analysis failed to impact clinical practice, not because the absolute gain was too small but because such an estimate was still imprecise, ranging from 1% detriment to a 10% benefit. In addition, the heterogeneity of surgical procedures and the difference in the staging modalities strongly limit the applicability of the results of this meta-analysis.

The results of the recently performed randomised trials support the conclusion that adjuvant chemotherapy confers survival advantage in early stage NSCLC [2–6] (Table 1).

These conclusions have been further supported by a recent meta-analysis of individual patient data – the Lung Adjuvant Cisplatin Evaluation (LACE) – in which data were pooled from four of the above mentioned studies and the Big Lung Trial (BLT) [7,8]. This analysis involved data from 4,584 patients with resected NSCLC who were randomised to adjuvant chemotherapy or no further systemic therapy. In some of these studies, adjuvant radiotherapy was used and left to the discretion of each participating centre. Adjuvant chemotherapy was associated with a significant benefit in overall survival; at 5 years, there was a 5.3% $\pm$ 1.6% absolute increase in survival in favour of adjuvant chemotherapy compared with no further systemic therapy. The overall benefit observed varied with stage; there was a significant benefit for patients with stage II and stage III disease whereas there was no significant benefit for those with stage IB disease and an apparent detrimental effect for those with stage IA disease.

In two of the positive studies for adjuvant chemotherapy [4,6], a combination of cisplatin and weekly vinorelbine prolonged survival. These findings led to the conclusion that cisplatin/vinorelbine is a regimen of choice for adjuvant therapies. However, in another adjuvant trial, the combination of cisplatin and vinorelbine did not perform significantly better than any other combination tested [2]. Moreover, when the combination of cisplatin plus a third-generation agent including taxanes, vinorelbine and gemcitabine are compared `head to head' in the metastatic or locally advanced settings, no significant differences in overall survival are observed.

In the same two studies [4,6] the use of adjuvant cisplatin/vinorelbine was associated with significant toxicity (severe neutropenia [grade 3/4] in >80% of patients and febrile neutropenia in >8–10% of patients) and only few patients could receive treatment as scheduled. Therefore, the schedule of administration of vinorelbine of these studies is not routinely used.

A meta-analysis of several Japanese studies of postoperative adjuvant chemotherapy reported a survival benefit in patients with stage I disease [9]. Of the 2,003 patients studied, 95% had stage I disease. Patients were randomised to receive an oral adjuvant treatment with tegafur in combination with uracil (UFT) for 2 years or no further treatment. The overall survival rates at 5- and 7-years were significantly greater in patients who had received adjuvant chemotherapy than in those who had received surgery alone (81.8% vs 76.5% at 5 years, $p = 0.011$; 77.2% vs 69.5% at 7 years, $p = 0.001$).

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 in clinical practice because of potential pharmacogenomic differences between Japanese and non-Japanese patients.

Currently, the available evidence suggests that the best candidates for adjuvant therapy are those patients who have undergone lobectomy, those who have made a complete recovery from surgery, have no severe comorbidities, are aged < 70 years and have a performance status of 0 or 1. Two further issues that need to be addressed in future research are the potential differences in survival between smokers and never smokers, and the effect on prognosis of the absence or presence of vascular invasion. It is becoming clear that tumours in non-smokers differ from those in smokers in terms of histology and possibly prognosis. This could have implications for the risk of recurrence and hence the value of adjuvant therapy. Similarly, the presence or absence of vascular invasion may influence the risk of recurrence and hence whether adjuvant therapy is likely to be beneficial.

Table 1 Results of adjuvant chemotherapy in patients with early-stage NSCLC [2–6]

Trial	Stage IA	Stage IB	Stage II	Stage IIIA
ALPI [2]	Negative	Negative	Negative	Negative
IALT [3]	Negative	Negative	Negative	Positive
NCIC [4]	Not Tested	Negative	Positive	Not tested
CALGB [5]	Not tested	Initially positive* Subsequently negative	Not tested	Not tested
ANITA [6]	Not tested	Negative	Positive	Positive

*Early data.

ALPI, Adjuvant Lung Cancer Project Italy; ANITA, Adjuvant Navelbine International Trialists Association; CALGB, Cancer and Leukaemia Group B; IALT, International Adjuvant Lung Cancer Trial; NCI-C, National Cancer Institute of Canada.

2. Identifying patients for adjuvant chemotherapy

It is clear that only some patients benefit from systemic adjuvant therapy. This is the group of patients who have residual micrometastases that are sensitive to adjuvant therapy. Patients with R0 resection of their tumour, without micrometastases are cured with local/regional therapy, whereas those with residual micrometastases that are resistant to adjuvant therapy do not respond to adjuvant therapy. There is therefore a need to identify factors that would allow for the identification of patients most likely to benefit from adjuvant chemotherapy.

A potential predictive marker of bone metastases has recently been identified in patients with completely resected NSCLC that is also associated with survival outcome [10]. We investigated the presence of 10 different markers involved in bone resorption or development of metastases in 30 patients with resected NSCLC who subsequently developed bone metastases, and compared the results of this patient group with those of 30 patients with resected NSCLC without metastases and of 26 patients with resected NSCLC who developed non-bone metastases. The expression of bone sialoprotein (BSP) was strongly correlated with the development of bone metastases ($p < 0.001$). Median survival was significantly shorter in patients expressing BSP compared with those not expressing BSP (25 vs 39 months, $p = 0.02$) (Fig. 1). These data suggest that patients with tumours expressing BSP are at high risk of developing bone metastases and may therefore be more likely to benefit from adjuvant chemotherapy or other preventive treatments.

Another approach to identifying patients most likely to benefit from adjuvant therapy is to use pharmacogenomics. This involves the analysis of molecular markers in tumours at the genetic level using polymerase chain reaction (PCR) techniques to analyse gene mutations and/or the level of gene expression. Various genetic markers that are predictive of increased or decreased sensitivity to various cytotoxic agents have been identified (Table 2) [11–13].

We performed a retrospective analysis of the expression of three genes and their potential correlation with survival in patients with advanced NSCLC treated with gemcitabine or gemcitabine/cisplatin [13]. The expression levels of excision repair cross-complementation 1 (*ERCC1*), ribonucleotide reductase M1 (*RRM1*) and epidermal growth factor receptor (*EGFR*) were determined by real-time PCR from 70 formalin-fixed, paraffin-embedded bronchoscopic/fine-needle aspiration biopsies. *ERCC1* and *RRM1* but not *EFGR*

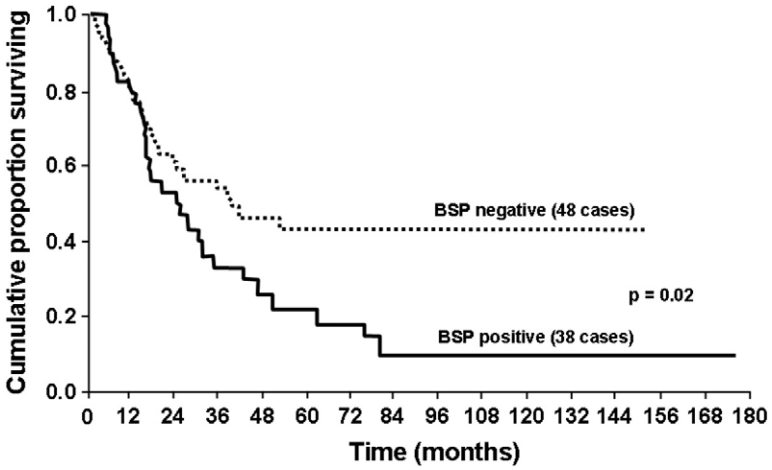

Figure 1 Median overall survival distribution of patients with non-small cell lung cancer according to the expression of bone sialoprotein (BSP). Adapted with permission from the American Society of Clinical Oncology [10].

Table 2 Molecular markers predictive of response to chemotherapy in NSCLC [11–13]

Gene	Abnormality	Drug	Response
p53	Mutation	Multiple	↓
K-ras	Mutation	Platinum	↓
HER-2	Increased expression	Multiple	↓
p27	Induced expression	Taxanes	↑
Beta tubulin	Increased isotype 3	Taxanes	↓
RRM1	Increased expression	Gemcitabine	↓
ERCC1	Increased expression	Platinum	↓
EGFR mutation	Present	Platinum	↑

EGFR, epidermal growth factor receptor; ERCC1, excision repair cross-complementation 1; HER-2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; RRM1, ribonucleotide reductase M1.

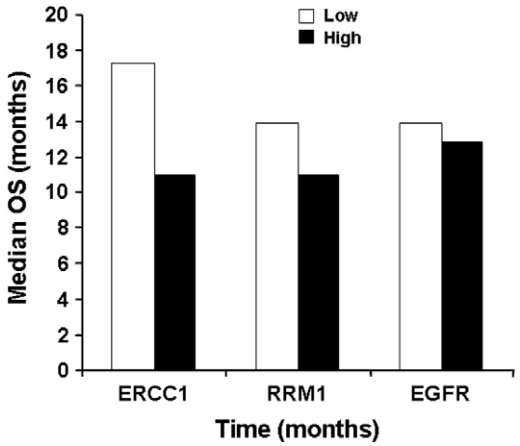

Figure 2 Median survival in patients with advanced non-small cell lung cancer according to levels of expression (low vs high) of *ERCC1* (p = 0.0032), *RRM1* (p = 0.0390) and *EGFR* (p < 0.452) [13]. EGFR, epidermal growth factor receptor; ERCC1, excision repair cross-complementation 1; OS, overall survival; RRM1, ribonucleotide reductase M1.

were strongly correlated with overall survival; low levels of *ERCC1* and *RRM1* expression were associated with a significantly longer survival compared to patients with higher levels of expression of these two genes (Fig. 2). These data suggest that *ERCC1* and *RRM1* are appropriate genetic markers that could be used to select patients likely to benefit from adjuvant therapy. Indeed, this approach is being used in an ongoing study in patients with stage IIIB/IV disease in which patients receive 1 of 4 different chemotherapy regimens according to the level of expression of *RRM1* and *ERCC1* on their tumours. This approach is expected to yield a superior overall survival compared with historical data in this patient population.

Another retrospective study investigated whether the expression of the *ERCC1* protein could be used to predict if a patient will benefit from adjuvant chemotherapy compared with no further treatment [14]. This study analysed data from the IALT in which patients were randomised to receive cisplatin-based chemotherapy or observation [3]. It was found that with adjuvant chemotherapy, survival was significantly longer in patients with ERCC1-negative tumours (adjusted hazard ratio [HR] 0.65, 95% CI 0.50–0.86, p = 0.002), but not in patients with ERCC1-positive tumours (adjusted HR 1.14, 95% CI 0.84–1.55, p = 0.40) [14]. However, for patients who did not receive adjuvant chemotherapy, survival was significantly longer in those with ERCC1-positive tumours compared to those with ERCC1-negative tumours (adjusted HR 0.66, 95% CI 0.49–0.90, p = 0.009). Thus, ERCC1 expression may be an independent predictor of the benefit of chemotherapy in patients with NSCLC.

The use of pharmacogenomics to predict response to therapy has been taken a step further by Potti et al. who have developed a model to predict therapeutic outcome based on gene expression profiles [15]. This technique involves analysis of total RNA from tumour cells, rather than following the expression of particular genes. Using this method, the authors developed a model that predicted disease recurrence with an overall accuracy of 93%, compared with 64% for a model based on clinical parameters (age, sex, tumour diameter, stage of disease, histological subtype and smoking history). When the accuracy of the pharmacogenomic model was assessed using data from two further studies, the accuracy was found to be 79% and 72%, thus validating the model. These data suggest that analysis of gene expression profiles can be used to predict patients for whom adjuvant chemotherapy may be appropriate.

This study also investigated whether the model based on gene expression profiles could be used to identify patients with stage IA disease at risk of recurrence. Previous studies have shown that approximately 25% of patients with stage IA disease have disease recurrence within 5 years, but markers for identifying such patients have not been developed. In this study, the model of gene expression profiles was used to identify patients with stage IA disease with a high or low risk of recurrence. Kaplan-Meier survival plots for the two subgroups revealed a 4-year survival of less than 10% for the high-risk group compared with approximately 90% for the low-risk group. These data suggest that analysis of gene expression profiles can be used to identify high- and low-risk groups of patients with stage IA disease. This information could help identify patients with stage IA disease for whom adjuvant chemotherapy may be appropriate.

On the basis of the findings from this study, the CALGB (study 30506) has developed a randomised phase II trial in which 138 patients with operable stage I disease will be assigned to a predicted outcome of low- or high-risk of recurrence by gene expression analysis. Patients identified as low risk will be observed according to standard practice. Those identified as high risk will be randomised to either adjuvant chemotherapy or observation only.

3. Targeted therapies

Another potential approach to improving the outcome for patients with early-stage NSCLC is the use of targeted therapies such as bevacizumab and erlotinib. Two ongoing studies are investigating the use of these therapies in the adjuvant setting. In the Eastern Cooperative Oncology Group (ECOG)/Intergroup Adjuvant Trial, patients with resected stage IB/IIIA-N2 disease are being randomised to receive platinum-based chemotherapy with or without bevacizumab. In the RADIANT study, patients with completely resected stage IB/IIIA disease are receiving 4 cycles of platinum-based chemotherapy and then being randomised to receive erlotinib or placebo for 2 years.

4. Neoadjuvant chemotherapy in operable NSCLC

Neoadjuvant chemotherapy may eventually have a role in early-stage NSCLC. A multicentre trial conducted by the French Thoracic Cooperative Group randomised 373 patients with resectable stage IB, II and IIIA NSCLC to undergo either surgery alone or chemotherapy (mitomycin, ifosfamide and cisplatin) at 3-week intervals for 2 cycles followed by surgery [16]. Overall, 355 eligible patients were randomised. A Cox multivariate analysis demon-

strated a longer 2-year overall survival rate in patients receiving neoadjuvant chemotherapy than in those receiving surgery alone (59% vs 52%). The most striking survival benefit was observed in patients with early-stage disease (either N0 or N1, p = 0.008) [16].

Several randomised neo-adjuvant studies have subsequently been performed, but most have been stopped before reaching the planned accrual because of the emerging positive results of adjuvant chemotherapy. An American Intergroup study (S9900) compared surgery alone with surgery plus preoperative chemotherapy with paclitaxel/carboplatin in patients with stage IB, II and selected IIIA NSCLC [17]. The study was prematurely closed after the inclusion of 354 patients. Preliminary results showed that neoadjuvant chemotherapy had a small, non-significant benefit on overall survival rate at 2 years compared with surgery alone (69% vs 63%). Of the other three studies, two have been completed, data of which will be presented soon, and another has been stopped prematurely. While data from these studies may help to clarify the value of neoadjuvant chemotherapy in this setting, data from studies on other solid tumours suggest that there is unlikely to be a significant difference in outcome between adjuvant and neoadjuvant chemotherapy.

5. Studies of pemetrexed in early-stage NSCLC

Several phase II studies are investigating the activity of pemetrexed in the treatment of early-stage NSCLC. Table 3 summarises the design and aims of some of these trials.

6. Conclusions

The results of large phase III studies consistently show that adjuvant chemotherapy in patients with resected early-stage NSCLC improves survival by approximately 5% at 5 years compared with no further treatment. This benefit appears to be mainly confined to patients with stage II or stage III disease, although it is clear that some patients with stage I disease are also at significant risk of relapse and thus might benefit from adjuvant therapy. The issue regarding the use of adjuvant therapy in early-stage NSCLC disease is thus being able to predict which patients are at risk of relapse and have chemotherapy-sensitive tumours, since these are the patients who could benefit from adjuvant chemotherapy.

Accumulating evidence suggests that molecular markers including the analysis of gene expression in tumour

Table 3 Summary of new phase II studies of pemetrexed in early-stage non-small cell lung cancer

Study status	Study design	Patients	Chemotherapy	Study aim
Recruiting: NCT00269152	Multicentre, open-label, two-arm, randomised, parallel	Stage IB, IIA or IIB n = 122 ongoing	Pemetrexed (+ B_{12}, folic acid) plus: • cisplatin • carboplatin	Clinical feasibility
Recruiting: NCT00349089	Randomised, open label, active control, parallel	Stage IB/IIIA n = 134 ongoing	4 cycles of adjuvant therapy: • pemetrexed/cisplatin (+ B_{12}, folic acid) • vinorelbine/cisplatin	Clinical feasibility
Recruiting: NCT00356525	Randomised, open label, uncontrolled, parallel	Relapsed, early-stage n = 160 ongoing	Relapse $<$ 1 year from chemotherapy randomised to: • pemetrexed/gemcitabine • pemetrexed Relapse $\geq$ 1 year from chemotherapy randomised to: • pemetrexed/gemcitabine • pemetrexed/carboplatin	Objective response rate
Development		Stage IB/IIIA	PET scan with SUV $\geq$ 7 followed by: • pemetrexed/cisplatin • pemetrexed/cisplatin + LMWH	
Development		Stage IB/IIIA	Gene expression analysis followed by: • pemetrexed/cisplatin • gemcitabine/cisplatin • pemetrexed/gemcitabine • docetaxel/cisplatin	

LMWH, low-molecular-weight heparin; NCT, ClinicalTrials.gov Identifier; PET, positron emission tomography; SUV, standardised uptake value.

cells may be of value in predicting patients at risk of relapse and therefore most likely to benefit from adjuvant chemotherapy. For example, expression of BSP, a protein involved in bone remodelling, correlates with the development of bone metastases, while expression of *ERCC1* and *RRM1* appear to correlate with survival following adjuvant chemotherapy. Gene expression analysis, which analyses total mRNA rather than the expression of individual genes, may be an even more powerful tool for identifying patients at risk or relapse. Indeed, this type of analysis was able to identify patients with stage IA disease at high risk of relapse who might therefore benefit from adjuvant therapy, in contrast to low-risk patients with stage IA disease. This pharmacogenomic approach offers the possibility of better patient selection for adjuvant chemotherapy and is a priority for future research.

Although a role for adjuvant chemotherapy is well established for patients with stage II/III disease, and possibly patients with stage IB disease, there is much interest in developing more effective regimens in this setting. Cisplatin/vinorelbine is recognised to be active, but, in the proven dosage in trials, a regimen that is too toxic. Studies are underway to investigate the possible benefits of newer cytotoxic agents such as pemetrexed, and targeted agents such as bevacizumab and erlotinib. The results of such studies, together with better patient selection, should help improve the survival benefit of approximately 5% at 5 years, currently achieved with adjuvant chemotherapy.

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Conflict of interest

The author is a consultant of Eli Lilly and has received honoraria from Eli Lilly, Astra Zeneca and Sanofi-Aventis.

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References

[1] Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Br Med J 1995;311:899–909.

[2] Scagliotti GV, Fossati R, Torri V, et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell Lung cancer. J Natl Cancer Inst 2003;95:1453–61.

[3] Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004;350:351–60.

[4] Winton TL, Livingston R, Johnson D, et al. Vinorelbine and cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005;352:2589–97.

[5] Strauss GM, Herndon JE, Maddaus MA, et al. Adjuvant chemotherapy in stage IB non-small cell lung cancer (NSCLC): update of Cancer And Leukemia Group B (CALGB) protocol 9633. J Clin Oncol 2006;24(18S):7007.

[6] Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB–IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006;7:719–27.

[7] Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation (LACE): a pooled analysis of five randomized clinical trials including 4,584 patients. J Clin Oncol 2006;24(18S):7008.

[8] Waller D, Peake MD, Stephens RJ, et al. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. Eur J Cardiothorac Surg 2004;26:173–82.

[9] Hamada C, Tanaka F, Ohta M, et al. Meta-analysis of postoperative adjuvant chemotherapy with tagfur-uracil in non-small-cell lung cancer. J Clin Oncol 2005;23:4999–5006.

[10] Papotti M, Kalebic T, Volante M, et al. Bone sialoprotein is predictive of bone metastases in resectable non-small-cell lung cancer: a retrospective case-control study. J Clin Oncol 2006;24:4818–24.

[11] Bepler G. Pharmacogenomics: a reality or still a promise? Lung Cancer 2006;54(Suppl 2):S3–7.

[12] Danesi R, De Braud F, Fogli S, et al. Pharmacogenetics of anticancer drug sensitivity in non-small cell lung cancer. Pharmacol Rev 2003;55:57–103.

[13] Ceppi P, Volante M, Novello S, et al. ERCC1 and RRM1 gene expressions but not EGFR are predictive of shorter survival in advanced non-small-cell lung cancer treated with cisplatin and gemcitabine. Ann Oncol 2006;17:1818–25.

[14] Olaussen KA, Dunant A, Fouret P, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med 2006;355:983–91.

[15] Potti A, Mukherjee S, Petersen R, et al. A genomic strategy to refine prognosis in early-stage non-small-cell lung cancer. N Engl J Med 2006;355:570–80.

[16] Depierre A, Milleron B, Moro-Sibilot, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. J Clin Oncol 2002;20:247–53.

[17] Pisters K, Vallieres P, Bunn J, et al. S9900: a phase III trial of surgery alone or surgery plus preoperative (preop) paclitaxel/carboplatin (PC) chemotherapy in early stage non-small cell lung cancer (NSCLC): preliminary results. J Clin Oncol 2005;23(16S):LBA 7012.