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TOPIC HIGHLIGHT

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Advances in adjuvant systemic therapy for non-small-cell lung cancer

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Abstract

Non-small-cell lung cancer remains a leading cause of death around the world. For most cases, the only chance of cure comes from resection for localised disease, however relapse rates remain high following surgery. Data has emerged over recent years regarding the utility of adjuvant chemotherapy for improving disease-free and overall survival of patients following curative resection. This paper reviews the clinical trials that have been conducted in this area along with the studies integrating radiation therapy in the adjuvant setting. The role of prognostic gene signatures are reviewed as well as ongoing clinical trials including those incorporating biological or targeted therapies.

Key words: Carcinoma; Non-small-cell lung; Chemotherapy; Adjuvant; Radiotherapy; Biological therapy; Biomarker

Core tip: Improvement in survivals of patients with resected non-small lung cancer has been rather modest. Adjuvant systemic chemotherapy with high dose cisplatin and vinorelbine has been established to be beneficial in improving disease free and overall survival in stage Ⅱ and ⅢA but not stage Ⅰ patients. This benefit is observed also in elderly patients. Post-operative radiation therapy has a deleterious effect on early stage tumour but appears to improve survival and reduce local recurrence in higher risk stage Ⅲ or N2 disease with modern techniques. The availability of targeted biologicals and biomarker development may allow future selection of high risk groups who benefit from adjuvant treatments.

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INTRODUCTION

Lung cancer remains the leading cause of cancer-related death, contributing 19.4% to the total number of cancer deaths worldwide in 2012[1]. Between 1975 and 2008 the 5-year survival for this condition in the United States has only seen a modest rise from 12% to 17%[2]. Non-small cell lung cancer (NSCLC) comprises approximately 80% of all lung cancers; despite surgery 5-year mortality ranges from 33% to 77% for stage Ⅰa and Ⅲa disease respectively, primarily from tumour recurrence[3]. Over the last few decades adjuvant chemotherapy following curative surgery has been proven to decrease recurrence and improve patient survival, initially for node-positive breast cancer[4] but subsequently to include other malignancies such as ovarian[5], bowel[6], gastro-oesophageal[7] and pancreatic[8] cancers. In addition, inhibitors of tumour growth signalling

pathways such as the anti-human epidermal growth factor receptor 2 (HER2) antibody trastuzumab for breast cancer[9], are starting to be incorporated into adjuvant systemic therapies.

Patient selection for adjuvant therapy is mainly based on the odds of tumour recurrence. Generally, patients with high recurrence risk will derive the most benefit from adjuvant therapy. Conversely, patients who have a low risk of relapse may not derive a net benefit from adjuvant therapy, particularly if the marginal reduction in relapse risk is not offset against the risks and inconveniences of treatment. Adjuvant radiation can also confer a benefit although this advantage is generally restricted to preventing locoregional tumour recurrence. This article reviews the evidence for adjuvant therapy for NSCLC with a focus on systemic treatments.

CHEMOTHERAPY

Alkylating agents

Initial studies of adjuvant chemotherapy for NSCLC were not promising. In 1995 a meta-analysis of adjuvant chemotherapy by the NSCLC Collaborative Group showed that alkylating agents used in the earliest adjuvant studies had a detrimental effect on survival over surgery alone, with a HR of 1.15 ($P = 0.005$)[10].

Early cisplatin trials

Despite the detrimental effect found with alkylating agents, the same meta-analysis suggested there may be a small survival benefit within the subgroup of trials that used cisplatin-based chemotherapy with a HR of 0.87 ($P = 0.08$); similarly there was a non-significant improvement in survival by 3% at 2 years, and 5% at 5 years, with treatment. The individual studies pooled to obtain this result were small, with sample sizes ranging from 28 to 332 patients.

Subsequent to this meta-analysis, the Eastern Cooperative Oncology Group (ECOG) 3590 study compared post-operative radiotherapy alone, to the same plus chemotherapy consisting of 4 cycles of cisplatin and etoposide on 488 patients[11]. After a median follow-up of 44 mo, there was no improvement in median survival between the arms, being 38 mo for chemotherapy and 39 mo for observation. Only 69% of patients assigned chemotherapy received all 4 cycles of treatment, and this included patients who required treatment dose reductions.

The Big Lung Trial (BLT)[12] was conducted to see if it could confirm the findings from the meta-analysis of a small survival advantage from adjuvant cisplatin-based chemotherapy. The design was pragmatic and clinicians could choose from 4 different cisplatin-based chemotherapy regimens; in addition chemotherapy could be administered either before or after surgery. This study closed early owing to slow accrual, reaching only 76% of the target of 500 patients. However even if full accrual were achieved, the sample size would still only have had 20% power to detect a 5% difference in survival.

The Adjuvant Lung Project Italy (ALPI) was the first large cisplatin-based adjuvant trial that had adequate statistical power to confirm the small benefits suggested by the 1995 meta-analysis[13]. It recruited patients with resected stage I -Ⅲ NSCLC between 1994 and 1999. Patients were randomised to receive 3 cycles of mitomycin, vindesine and cisplatin, or observation. Radiation was permitted in accordance with the policy of each treating institution.

After a median follow up of 64.5 mo, no advantage was seen in the chemotherapy arm for either overall survival or disease-free survival. Possible explanations for the negative result include the removal of 1 centre which recruited 108 of the total of 1209 patients owing to concerns over data integrity and low treatment compliance, with only 69% completing the 3 cycles of chemotherapy. Furthermore, about half of these patients required dose reductions. However, analyses adjusting for these effects still did not suggest that they were responsible for the negative result. Another possible explanation is the imbalance in radiation delivery favouring the control arm, as 26% of patients in the chemo arm had their radiation interrupted at an early stage compared to 11% of controls.

Recent cisplatin trials

The largest adjuvant lung cancer study to date is the International Adjuvant Lung Trial (IALT)[14]. The study included 1867 patients with completely resected stage I -Ⅲ NSCLC who were randomly assigned to 3-4 cycles of cisplatin-based chemotherapy or observation. This was a pragmatic study, with participating centres being allowed to choose from 4 chemotherapy regimens (details in Table 1). Post-operative radiotherapy was permitted in accordance to local institutional policy. At a median follow up of 56 mo, there was a statistically significant overall survival benefit from chemotherapy [hazzd ratio (HR), 0.86; $P < 0.03$]. The 2-year survival rate was 70.3% in the chemotherapy group and 66.7% in the control group and at 5-years, this was 44.5% and 40.4%, respectively. Similarly, disease-free survival was significantly better in chemotherapy arm with a HR of 0.83 ($P < 0.03$).

An updated analysis of this study was published with a median follow up period of 7.5 years[15]. The benefit seen earlier was maintained for overall survival (HR, 0.91; $P = 0.10$) and disease-free survival (HR, 0.88; $P = 0.02$). However there was an increase in late mortality seen after 5 years of follow-up (HR, 1.45; $P = 0.04$) with a positive test for interaction ($P = 0.006$). An increase in non-lung-cancer mortality was observed in the chemotherapy arm (HR, 1.34; $P = 0.06$), and probably explains the late mortality, as there was no evidence of an interaction between chemotherapy effect and the follow-up period. The statistically significant causes of non-cancer deaths were infections, circulatory and respiratory diseases.

The JBR.10 trial[16] was a large North American

Table 1 Important randomised trials of adjuvant treatments for non-small cell lung cancer

Ref.	Size	Stage	[1]Chemotherapy regimen	OS	DFS
IALT[14]	1867	I -Ⅲ	Pragmatic study of 3-4 cycles of cisplatin (80-100 mg/m^2 on D1) with either: vindesine 3 mg/m^2 weekly; vinblastine 4 mg/m^2 weekly; vinorelbine 30 mg/m^2 weekly; etoposide 100 mg/m^2 D1-3	4.1% absolute benefit at 5 yr (HR, 0.86; $P < 0.03$)	5.1% absolute benefit at 5 yr (HR, 0.83; $P < 0.003$)
NCIC JBR.10[16]	482	I b-II	4 cycles of: cisplatin 50 mg/m^2 D1 + 8; vinorelbine 25 mg/m^2 D1, 8, 15, 22 in a 4-wk cycle	15% absolute benefit at 5 yr ($P = 0.04$)	12% absolute benefit at 5 yr ($P = 0.08$)
ANITA[18]	840	Stage I b-Ⅲa	4 cycles of: cisplatin 100 mg/m^2 D1; vinorelbine 30 mg/m^2 D1, 8, 15, 22 in a 4-wk cycle	8.6% absolute benefit at 5 yr ($P = 0.17$ for HR)	8.7% absolute benefit at 5 yr ($P = 0.002$ for HR)
JLCRG[24]	999	I	Daily UFT as tegafur 250 mg/m^2 per day plus uracil, for 2 yr	3% absolute benefit at 5 yr ($P = 0.04$)	NR
NCIC BR19[30]	1242	I b-Ⅲa	Gefitinib 250 mg daily for 2 yr	HR, 1.24 ($P = 0.14$)	HR, 1.22 ($P = 0.15$)
CALGB 9633[16]	344	I b	4 cycles of carboplatin AUC 6 plus paclitaxel 200 mg/m^2, every 3 wk	HR, 0.83 ($P = 0.12$)	HR, 0.80 ($P = 0.065$)

[1]Control arms treated with observation. OS: Overall survival; DFS: Disease-free survival; HR: Hazard ratio; NR: Not reported.

Intergroup adjuvant study of stage I b and Ⅱ NSCLC. Chemotherapy consisted of 4 cycles of cisplatin plus vinorelbine, and radiation was not permitted. The results of this study strongly favoured chemotherapy, with a 5-year survival rate of 69% compared to 54% in the control arm ($P = 0.03$). The HR for death was 0.69 ($P = 0.04$). Similarly, 5-year disease-free survival rates were 61% and 49% for the study and control arms, respectively ($P = 0.08$).

The results of this study were updated after a median follow up of 9.3 years[17]. Reassuringly, the improvement in overall survival from chemotherapy was maintained with a HR of 0.78 ($P = 0.04$) and 0.73 ($P = 0.03$) for overall survival and disease-free survival, respectively. Five-year survival rates were 67% in the chemotherapy arm and 56 % in the control arm. The benefit was confined to stage Ⅱ patients, with a HR of 0.68 (95%CI: 0.5-0.92, $P = 0.01$) compared to 1.03 (95%CI: 0.7-1.52, $P = 0.87$) for stage I b patients where there is no benefit, in addition there was a trend for interaction with disease stage ($P = 0.09$).

The Adjuvant Navelbine International Trialist Association (ANITA) conducted a very similar study with equally similar results[18], thus validating the strongly positive findings from JBR.10. In contrast to the JBR.10 study, patients with stage Ⅲ NSCLC were included in the ANITA trial in addition to stages I b and Ⅱ. Patients were randomised to receive 4 cycles of chemotherapy with cisplatin plus vinorelbine, or observation. After a median follow-up of 76 mo, there was an improvement in overall survival (HR, 0.8; $P = 0.017$) with chemotherapy. Median survival in the chemotherapy group was 65.7 mo compared to 43.7 mo in the control group. There was an absolute benefit from chemotherapy on overall survival of 8.4% at 7 years, however stage I b patients did not benefit from treatment with a HR for survival of 1.1 (95%CI: 0.76-1.57). In parallel with the JBR.10 findings, the ANITA study also found a trend towards an interaction between tumour stage and chemotherapy ($P = 0.07$).

Individual patient data from the 5 largest randomised trials of cisplatin-based chemotherapy were pooled in another meta-analysis in an attempt to verify the small but not statistically significant improvement in survival seen earlier by the Collaborative Group. The Lung Adjuvant Cisplatin Evaluation (LACE)[19] reassuringly confirms a significant survival benefit (HR, 0.89; $P = 0.005$) and disease-free survival benefit (HR, 0.84; $P = 0.001$) from adjuvant chemotherapy. The absolute benefit at 5 years was 5.4% and 5.8% for overall and disease-free survival, respectively. There was no heterogeneity of chemotherapy effect between the trials. In parallel with the updated IALT analysis, there was a similar increase in non-lung-cancer deaths in the chemotherapy arm, particularly in the first 6 mo of follow-up, with a HR of 2.41 ($P < 0.001$). Of these 74 deaths seen in the chemotherapy arm, 18 were from chemotherapy toxicity. Another 40 deaths in this arm were from pulmonary/cardiovascular events, compared to 21 in the control arm. The authors hypothesized that some of these excess cardiovascular deaths seen in the chemotherapy arm could be a result of cisplatin, particularly as the under-reporting of cardiovascular complications from cisplatin has been described in the literature[20].

The NSCLC Meta-analyses Collaborative Group updated their previous results[10] by performing 2 further meta-analyses[21]. The first examined the benefit of adding chemotherapy to surgery. Similarly, the second analysis explored the benefit of chemotherapy, but in the setting of surgery plus radiotherapy as the control. Both these meta-analyses showed a benefit from adjuvant chemotherapy, with good concordance in survival HRs (for surgery, HR, 0.86; $P < 0.0001$; for surgery plus radiotherapy, HR, 0.85; $P = 0.009$) and also the absolute improvement in 5-year survival (4% for both).

Uracil-tegafur

The antimetabolite uracil-tegafur (UFT) has been

studied in Japan for the treatment of NSCLC. It is an orally administered combination of uracil and tegafur (a pro-drug of fluorouracil) and demonstrated single-agent activity against NSCLC as well as in combination with cisplatin[22]. A small adjuvant study performed by the West Japan Study Group for Lung Cancer reported improved survival for the 2 arms that received adjuvant UFT-based chemotherapy *vs* observation[23] and paved the way to a large confirmatory trial by the Japan Lung Cancer Research Group[24]. Recruitment was restricted to patients with stage I adenocarcinoma and chemotherapy consisted of 2 years of UFT. With a median follow up of 72 mo the 5-year survival for the chemotherapy arm was 88% in the chemotherapy arm *vs* 85% in the observational group (P = 0.047). This advantage was driven by an 11% absolute improvement in 5-year survival for patients with T2 tumours (P - 0.005), whereas the difference in 5-year survival for patients with T1 tumours was only 1%.

Not all trials of adjuvant UFT have been positive, hence the second Collaborative Group meta-analysis[20] pooled the results of 7 adjuvant studies that used tegafur/UFT as a single agent and found a survival benefit from treatment with a HR of 0.76 (P = 0.001). It also found a benefit for tegafur/UFT in combination with platinum, where the results of 8 pooled studies showed a HR of 0.79 (P = 0.005). Another meta-analysis restricted to studies using UFT alone showed a similar survival HR of 0.74 (P = 0.001)[25]. The absolute improvements in 5- and 7-year survival were 4.3% and 7.0%, respectively, however it should be noted that there is considerable overlap in the studies pooled between these meta-analyses.

UFT has only been widely studied for NSCLC in Japan, where ethnic differences in pharmacogenomics and tumour biology may mean that these findings may not be generalisable to NSCLC patients worldwide[26]. This suspicion is also heightened by the knowledge that its analog, fluorouracil, is generally considered to be ineffective against NSCLC. Lastly, adjuvant UFT has only been studied in a population that is made up almost exclusively of patients with stage I NSCLC, where the benefits from adjuvant cisplatin-based chemotherapy are still controversial. For these reasons UFT should not be considered a standard treatment for this setting, outside Japan.

TARGETED THERAPY

The epidermal growth factor receptor (EGFR) forms part of a signalling pathway that regulates a large range of cellular functions, including proliferation, invasion, angiogenesis and metastasis. It is commonly overexpressed in NSCLC. Trials of EGFR inhibitors showed activity in advanced NSCLC[27-29] and in 2002 the NCIC instigated the BR19 study to compare the EGFR inhibitor gefitinib with placebo in the adjuvant setting[30]. However, this study was closed prematurely in 2005, after the large ISEL study failed to show an improvement in overall survival from gefitinib for advanced NSCLC[31]. By then it had only accrued 503 patients out of a target of 1242. With a median follow-up period of 4.7 years, this study did not find a benefit in disease-free survival (HR, 1.22; P = 0.15) or overall survival (HR, 1.24; P = 0.14).

In light of current knowledge that activating mutations in the EGFR gene strongly correlate with responsiveness to getifinib[32,33], it is possible that the negative result of this study is related to the unusually low incidence of EGFR mutations found in this cohort, being detected in only 4% of the 359 tumour samples tested. The results of ongoing adjuvant studies of EGFR inhibitors in selected patients with EGFR-mutant tumours are awaited with interest, and are discussed towards the end of this article under "Ongoing studies". Targeted therapies will no doubt shape the future of oncology and are discussed further in that section. Table 1 summarises the important individual studies covered in this section and provides further details on their respective treatment regimens.

CHOICE OF REGIMEN

The 2 trials showing the largest magnitude of benefit from adjuvant chemotherapy to date are JBR.10[16] and ANITA[18], with treatment providing similar improvements in median survival of 21 and 22 mo, respectively. The use of nearly identical doses of chemotherapy (high-dose cisplatin plus weekly vinorelbine for 4 cycles) in these trials provides further validation of the effectiveness of this combination. Both studies used 100 mg/m^2 cisplatin per cycle; in ANITA this was given as a single dose on day 1 whereas it was divided into 2 doses of 50 mg/m^2 given on days 1 and 8 in JBR.10. Both studies used vinorelbine 30 mg/m^2 for 16 weekly doses at the onset, however the dose was subsequently reduced to 25 mg/m^2 in JBR.10 owing to a high incidence of treatment-related adverse events following the commencement of this study. While the efficacy of chemotherapy in both studies were comparable, the early treatment-related mortality in the ANITA trial was relatively high at 2% justifying the decision by the JBR.10 investigators to reduce the dose is justified. The incidence of clinically significant toxicities from cisplatin and vinorelbine in both these studies can be found in Table 2.

The Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis[19] confirmed the superiority of cisplatin plus vinorelbine over 2 other chemotherapy regimen subgroups (P = 0.04), but only when these subgroups were pooled together. There was also a trend in favour of a total cisplatin dose above 300 mg/m^2.

PATIENT SELECTION

The modest survival benefit obtained from ACT means that most patients will not personally benefit from the treatment. For instance, the 5% survival benefit from chemotherapy seen in the LACE meta-analysis would

Table 2 Incidence of treatment-related World Health Organization grade 3-4 toxicity from adjuvant cisplatin and vinorelbine

Trial	JBR.10 (%)[16]	ANITA (%)[18]
Anaemia	14	7
Thrombocytopenia	3	1
Neutropenia	85	73
Febrile neutropenia	9	7
Infection	11	1
Nausea/vomiting	27	10-17[1]
Diarrhoea	2	< 1
Constipation	5	3
Anorexia	15	10
Asthenia/fatigue	28	15
Peripheral neuropathy	3	3-7[2]
Creatinine elevation	(NR)[3]	< 1
Treatment-related mortality[4]	0.8	2

[1]Separately documented as nausea (10%) and vomiting (7%) in publication; [2]Separately documented as hearing loss (2%), sensory neuropathy (2%) and motor neuropathy (3%) in publication; [3]NR: Not reported; [4]No WHO grade.

mean that 20 patients would need to be treated with chemotherapy to prevent 1 lung cancer death, whilst the other 19 patients would not derive any individual benefit from the treatment. Furthermore patients and clinicians also have to weigh up the risks and inconveniences of ACT. Cisplatin is considered to be strongly emetogenic, even though the current availability of 5HT$_3$ and substance P neurokinin-1 receptor antagonists have substantially reduced the magnitude of this side-effect. It also has the potential to cause permanent neuropathy that can be disabling in a small percentage of patients. Cardiovascular complications have been identified from cisplatin[19] and as mentioned above an increase in cardiovascular-related mortality has been identified in the chemotherapy cohort of the LACE meta-analysis[19]. For these reasons, it would be desirable to be able to accurately identify subgroups of NSCLC patients who would derive the greatest benefit from ACT.

Stage 1 disease

Hitherto all major adjuvant trials in NSCLC have used tumour stage as the criterion for selecting high-risk patients. Whilst adjuvant chemotherapy has become standard treatment for stages Ⅱ and Ⅲ NSCLC, it remains controversial for stage Ⅰ tumours. The cohorts in the 2 meta-analyses of adjuvant UFT trials[20,24] are almost exclusively made up of stage Ⅰ lung adenocarcinomas within the Japanese population. Given their positive findings, they vindicate treatment with UFT in this population, however there are no studies confirming this approach to be effective outside Japan.

Stage 1A: Only a small number of stage Ⅰ a patients have been entered into trials of adjuvant chemotherapy. In the LACE meta-analysis[19] stage Ⅰ a patients comprised 7% (347/4584) of the cohort; the HR for overall survival in this subgroup was 1.4 (95%CI: 0.95-2.06). The second Collaborative Group meta-analysis[20] collectively analysed 2058 cases with stage Ⅰ a disease within their total cohort of 8447 patients; the HR for survival in this subgroup was 1.19 (95%CI: 0.84-1.68).

Stage 1B: Subset analyses of the IALT[14], JBR.10[16] and ANITA[18] trials failed to show a benefit from chemotherapy for Stage 1b NSCLC. As discussed above, this is further reinforced by finding a trend towards an interaction between chemotherapy effect and disease stage in the updated JBR.10[17] and ANITA trials. The LACE meta-analysis[19] failed to show a benefit for stage Ⅰ b tumours (HR, 0.93; 95%CI: 0.78-1.10), although the second Collaborative Group meta-analysis[20] found survival HRs to be similar across stages Ⅰ b-Ⅲ NSCLC.

The Cancer and Leukemia Group B (CALGB) 9633 trial[34] is the only adjuvant study of a pure population of stage Ⅰ b NSCLC. It is also unique for its use of carboplatin instead of cisplatin. Three hundred and eighty-four patients were randomised to receive carboplatin plus paclitaxel, or observation. The preliminary results[35] after a median follow-up of 34 mo were promising and showed an improvement in overall survival (HR, 0.62; P = 0.028) with chemotherapy. However the mature analysis after a median follow-up of 74 mo no longer showed a statistically significant survival benefit (HR, 0.83; 90%CI: 0.64-1.08' P = 0.12) or disease-free survival benefit (HR, 0.80; 90%CI: 0.62-1.02, P = 0.065). Exploratory subgroup analysis of the CALGB 9633 results demonstrated a survival advantage from adjuvant chemotherapy for patients with tumours ≥ 4 cm in diameter (HR, 0.69; P = 0.043). Similar conclusions were found in the JBR.10 study where stage Ⅰ b tumours ≥ 4cm derived benefit from chemotherapy. In 2011 the IASLC re-classified stage Ⅰ b tumours which are ≥ 5 cm to be stage Ⅱ[36]. Given that at least half of the stage Ⅰ b patients in both the JBR.10 and CALGB 9633 cohorts had tumours ≥ 4 cm, a significant proportion of these cases will now thus be considered to have have stage Ⅱ disease, casting further doubt on the benefit of adjuvant chemotherapy for currently diagnosed stage Ⅰ b tumours.

Age

As the world population continues to age, the elderly will comprise an increasing proportion of patients with NSCLC. Despite this they are poorly represented in clinical trials; in the LACE meta-analysis[19] only 9% of patients were 70 years and older, yet this is close to the median age of diagnosis for NSCLC. This meta-analysis did not show evidence of an interaction between age and chemotherapy benefit.

A retrospective study evaluated the effect of age on adjuvant chemotherapy delivery, toxicity and survival in the JBR.10 study cohort[37]. Patients were dichotomised using a cut-off age of 65 to define the elderly. The survival HR for adjuvant chemotherapy in the older age group was 0.61 (P = 0.04) which was similar to the treatment effect in the overall study population (HR, 0.69). There was no evidence of an interaction by age group.

This benefit was observed despite the authors finding that the older patients received less and lower doses of chemotherapy. It was also reassuring that there was no evidence that the older cohort had increased toxicities from undergoing chemotherapy.

A population-based study in Ontario compared survival for resected NSCLC cases diagnosed between 2001 and 2006; in 2004 adjuvant chemotherapy was adopted across Canada's universal health insurance program[38]. Cases were identified using the Ontario Cancer Registry. This study found that only 16.2% of patients 70 years and older received adjuvant chemotherapy, compared to 42.7% of patients younger than 70. Despite this a small increase in 4-year survival from 47.1% to 49.9% could still be observed over this time period for patients 70 years and over (HR, 0.87; $P = 0.0123$). The adoption of chemotherapy was considered likely to have contributed to this improvement. Hence current evidence favours treating fit elderly patients with adjuvant chemotherapy.

Risk assessment models

An interactive online tool that uses clinicopathological variables to calculate an individual patient's relapse risk for NSCLC is available at www.adjuvantonline.com. It also calculates the estimated benefit of adjuvant chemotherapy and communicates the benefit of adjuvant chemotherapy in a format that is easy for patients and clinicians to comprehend. However, it should be noted that the ADJUVANT! model has only undergone external validation for its ability to predict recurrence for breast cancer in North American cohorts[39].

Histology

A differential response to chemotherapy based on histologic subtype has been observed in advanced NSCLC. In this setting a large randomised study[40] compared cisplatin and gemcitabine with cisplatin and pemetrexed and did not find a difference in overall survival between the treatment arms. However a pre-specified analysis showed that patients with adenocarcinoma and large cell carcinoma histology in the pemetrexed arm had improved survival. Pooled together into a "nonsquamous" subgroup by histology, their survival HR was 0.81 ($P = 0.005$). The treatment-by-histology interaction analysis ($P = 0.0011$) also showed that overall survival for patients with nonsquamous histology was significantly improved in the cisplatin/pemetrexed arm compared with the overall survival for patients treated with cisplatin/gemcitabine, or patients with squamous histology. This differential response to pemetrexed by histology was confirmed by re-analysing an older randomised study comparing pemetrexed and docetaxel in previously treated advanced NSCLC[41], plus another study comparing maintenance pemetrexed to placebo[42].

Hitherto no randomised adjuvant study on NSCLC has directly tested the effect of optimising chemotherapy by tumour histology in a similar manner. However, in the ongoing TASTE trial[43] that restricts entry to non-squamous tumours, all patients allocated to chemotherapy will receive cisplatin and pemetrexed. This trial is discussed further under "Ongoing studies".

Biomarkers

Tissue biomarkers can provide additional prognostic information to the existing clinico-pathological tumour staging information, and thus help with patient selection for adjuvant therapy. For example it may identify a subgroup of high-risk stage I patients who could benefit from adjuvant chemotherapy. In this section it is useful to note the distinction between prognostic and predictive biomarkers: a prognostic biomarker only provides information about cancer outcomes, regardless of therapy; on the other hand a predictive biomarker only gives information about the effect of a therapeutic intervention, independent of relapse risk[44].

Excision repair cross-complementation group 1: The International Adjuvant Lung Cancer Trial Biology (IALT Bio) study[45] examined whether immunohistochemistry (IHC) of lung cancer tissue of patients in the IALT trial (discussed above) could be used to determine which patients would obtain a benefit from cisplatin-based chemotherapy. The excision repair cross-complementation group 1 ERCC1 enzyme is critical for repairing cisplatin-mediated DNA damage, and overexpression has been linked to platinum resistance in tumour cell lines that include NSCLC. Using IHC, ERCC1 expression was evaluated retrospectively in a cohort of 783 patients of the 1045 enrolled in the original clinical trial. It found that patients whose tumours were ERCC1 negative had better overall survival with chemotherapy compared to the control group, with five-year survival being 47% *vs* 39% respectively (HR, 0.65; $P = 0.002$). Disease-free survival was also better with chemotherapy in this group compared to controls (HR, 0.65; $P = 0.001$). With ERCC1 positive tumours however, no significant difference was seen in overall survival between the chemotherapy and observation groups.

A systematic review and meta-analysis was conducted in 2011 to look at the prognostic and predictive utility of ERCC1 in lung cancer[46]. This found considerable methodological weaknesses in published studies with variations in ERCC1 cutoff, lack of proven correlation between quantitative reverse-transcriptase quantitative polymerase chain reaction (RT-qPCR) assays with IHC, non-standardised protocols and inadequate study sample sizes. It did not find ERCC1 expression to be prognostic in metastatic NSCLC, however there was tentative evidence that high levels of ERCC1 expression predicted resistance to platinum-based chemotherapy. Consequently such patients had shorter survival and a reduced likelihood of tumour response compared to those with low levels of ERCC1 expression. The authors concluded that ERCC1 should only be considered a predictive NSCLC biomarker but not prognostic. They also recommended that ERCC1 should not be used

routinely in clinical decision making until adequately powered prospective trials are conducted.

The ERCC1 Targeted trial was a prospective adjuvant study that used ERCC1 to optimise chemotherapy. It was prematurely terminated as the antibody used did not appear prognostic/predictive based on interim results[47].

Gene signatures: Gene expression profiling aims to identify unique "signatures" within the tumour's genome that can help predict relapse risk, response to treatment, or both.

A 15-gene signature was identified in the cohort entered into the JBR.10 trial (discussed above) that was both prognostic and predictive[48]. Microarray profiling was performed on 133 frozen tumour specimens collected from 482 patients enrolled in this study, to separate patients into a high and low risk group. Subsequently RT-qPCR was used in the same study to verify the microarray signature in this cohort, plus 30 additional cases from the study that were not profiled by microarray.

The prognostic value of this signature was tested using the cohort of patients randomised to observation, by dichotomising patients into high-risk and low-risk subgroups. Overall survival was significantly different between these subgroups, with a HR of 15.02 ($P < 0.001$) for patients whose tumours presented the signature. This finding was validated using 4 separate microarray datasets, and also subsequently using PCR on additional patients from the JBR.10 observation cohort.

This signature also had predictive value; high-risk patients derived a survival benefit from adjuvant chemotherapy (HR, 0.33; 95%CI: 0.17-0.63, $P = 0.005$) that was not seen with low-risk patients (HR, 3.67; 95%CI: 1.22-11.06, $P = 0.0133$). Additionally, although subgroup analysis in the original (clinical) trial found no benefit from chemotherapy in stage I B patients, this gene signature identified patients from this subgroup that had a survival benefit with adjuvant cisplatin and vinorelbine (HR, 0.44; 95%CI: 0.18-1.09, $P = 0.07$). Recently the signature has been validated in another independent cohort of 181 stage I and II patients[49]. Furthermore, this study found that it was prognostic for survival in both adenocarcinoma and squamous cell carcinoma subtypes, as well as a subgroup of 48 stage I a patients where the survival HR was 5.61 (95%CI: 1.19-26.45, $P = 0.014$).

Another signature incorporating 14 genes has been developed by a United States-Chinese group using formalin-fixed paraffin-embedded (FFPE) specimens in a cohort of 361 patients from the University of California San Francisco with resected non-squamous NSCLC[50]. This signature separated patients into low, intermediate and high-risk groups in terms of 5-year mortality. It was validated using 2 separate cohorts. The first was from Kaiser Permanente Northern California (N = 433), where multivariate analysis confirmed a survival HR of 2.04 ($P = 0.0016$) and 1.66 ($P = 0.0436$) for the high- and intermediate-risk groups, respectively. Using a China Clinical Trials Consortium dataset (N = 1006), corresponding survival HRs were 2.37 ($P < 0.0001$) and 1.87 ($P = 0.0354$). The strengths of this method is that it uses FFPE tissue and qPCR which are easily available in the clinical setting, while the large validation cohorts from diverse geographical and ethnic backgrounds which enables better generalisability of the results. A prospective study is planned to compare adjuvant chemotherapy *vs* observation in stage I patients identified as high risk, using this signature.

A 61-gene signature has been identified that is predictive of a benefit from the MAGE-A3 vaccine that is currently being studied in metastatic melanoma and early NSCLC[51]. This signature, determined by RT-qPCR, was developed using tumour samples from the melanoma cohort, where it was found to correlate with improved survival. The genes in this signature correlate with immune pathways involved in tissue-specific destruction such as interferon stimulated genes, CCR5 ligand, specific chemokine genes and immune effector function genes. The MAGE-A3 vaccine is concurrently being studied in the adjuvant setting for NSCLC and this is discussed further under "Ongoing studies". Hence this molecular study also tested the gene signature for its utility as a predictive marker for NSCLC, using tumour samples from the adjuvant studies. Its presence correlated with an improved disease-free interval with vaccine treatment with a HR of 0.42 (95%CI: 0.17-1.03, $P = 0.06$).

At the time of writing, no biomarker has been prospectively validated for the adjuvant management of NSCLC[52]. We predict that it is highly likely that EGFR (discussed in this article under "Targeted therapy" and "Ongoing studies"), currently used routinely in clinical practice as a predictive biomarker for advanced NSCLC, will also become a standard predictive biomarker for adjuvant therapy in the near future.

Individual preferences

The Preferences for Adjuvant ChemoTherapy (PACT) study surveyed 122 patients[53] following resection for early NSCLC, and also their 82 respective cancer clinicians[54] (medical oncologists and thoracic surgeons) to gauge the minimum survival benefit deemed necessary for them to be willing to undergo adjuvant chemotherapy. It found that the median values for the benefit to justify having chemotherapy were an increase in survival of 9 mo, alternatively a 5% increase in 3- or 5-year survival. These median values were similar between patients and clinicians, however the ranges varied widely between respondents, and even more so within the patient cohort. Compared to similar surveys for breast and colon cancer by the same authors, comparatively larger benefits were deemed necessary to justify having chemotherapy in this NSCLC cohort.

INTEGRATING ADJUVANT RADIATION

Post-operative radiotherapy (PORT) for NSCLC has been explored in multiple clinical trials which have yielded

conflicting results. A meta-analysis that included 2128 patients enrolled in nine randomised trials evaluating PORT *vs* surgery alone in resected NSCLC was published in 1998 and showed a significant detrimental effect of PORT on survival (HR, 1.21) with a 7% absolute reduction in overall survival at two years from 55% to 48% (P = 0.001)[55]. On sub-group analysis, this adverse effect was greatest for patients with stage Ⅰ-Ⅱ disease, whereas for those with stage Ⅲ disease there was no clear evidence of an adverse effect. This overview was updated in 2005 and still showed PORT to be detrimental with an 18% relative increase in the risk of death[56].

The results of this meta-analysis are subject to a number of important limitations. The study included patients enrolled from 1966-1997, many of whom were treated with older radiotherapy techniques (including Cobalt machines) no longer consistent with current standards. The staging evaluation was variable and the analysis included a large number of early stage patients (approximately 25% had N0 tumours) not expected to benefit from PORT. Up to 30% of patients came from a single study[57] where large dose per fraction (2.5Gy) and high total doses (up to 60Gy) were allowed which may have contributed to excess toxicity and decreased survival. A retrospective analysis of 7465 patients with stage Ⅱ or Ⅲ NSCLC from the Surveillance, Epidemiology and End Results (SEER) database between 1988-2002 confirms the findings of the meta-analysis[58]. It found that PORT significantly decreased the 5-year survival rate in patients with N0 or N1 disease. However, patients with N2 disease had significantly higher 5-year survival with PORT (27% *vs* 20%, P = 0.0077).

Subsequent to the meta-analysis, adjuvant chemotherapy has become standard treatment for high-risk NSCLC. Additionally, there have been significant technical improvements in radiotherapy planning and delivery in the modern era including CT-based conformal planning which have made it possible to deliver radiation more safely and with greater precision. Four D-CT planning and respiratory gating now make it possible to control for respiratory motion, potentially reducing pulmonary toxicity. It is difficult to know if these advances in radiation techniques will lead to better outcomes as there are no recent randomised studies published on this, however a recent meta-analysis of "modern" PORT for stage Ⅲ NSCLC reported an estimated absolute improvement in overall survival by 13% at 5 years and reduction in local recurrence as first relapse to 10%[59].

Hence the salient question to current practice is whether there is a role for adjuvant radiation using contemporaneous techniques, in conjunction with adjuvant chemotherapy. To answer this question, the investigators of the positive ANITA trial of adjuvant vinorelbine plus cisplatin (discussed above) have published a subsequent retrospective analysis on the effect of PORT from this study[60]. PORT was permitted in this trial in accordance with local institutional policy.An improvement in survival was seen for patients with N2 disease who received radiotherapy with a median survival 47 mo *vs* 24 mo in patients given adjuvant chemotherapy, and 23 mo *vs* 16 mo respectively for the observation cohort. Conversely, patients with N0 or N1 disease had a significant detriment in survival through the addition of PORT. Whilst these findings concur with the meta-analysis and SEER findings, the unexpectedly large improvements in survival found in this study should be interpreted with some caution, particularly taking into account the retrospective nature of the analysis, and that radiation was allocated in this study by institutional policy and not randomisation.

The Lung Adjuvant Radiotherapy (LungART) trial[61] is an ongoing international phase Ⅲ study comparing PORT with observation following surgery and chemotherapy and will directly answer the important question on whether there is a benefit from radiotherapy after resection for stage Ⅲ NSCLC.

Whilst survival is a key outcome when considering PORT, loco-regional control remains an important endpoint. The PORT meta-analysis provided data regarding local recurrence rates (LRR) for all included trials. There were fewer local recurrences but more deaths for PORT compared with surgery alone (N = 195 for PORT local recurrences *vs* 276 for surgery alone). However when the data were adjusted for the reduced survival, radiation was in fact found to be detrimental for local recurrence, with a HR of 1.16 (95%CI: 1.05-1.29, P = 0.005) favouring surgery alone. One study found no difference in LRR for 728 patients with completely resected NSCLC randomised to receive PORT (HR, 0.85; 95%CI: 0.64-1.14) or observation[57]. Another study reported a significant overall reduction in LRR at the bronchial stump and/or mediastinum in the group randomised to PORT[62]. A number of other studies have also reported a reduction in LRR favouring PORT[59,63,64]. PORT should therefore be considered in the setting of close or involved surgical margins where the rate of local recurrence is high[65].

The optimal sequence for integrating adjuvant chemotherapy and radiotherapy has not been established. A sequential approach delivering chemotherapy followed by radiotherapy has generally been favoured, although this is not supported by any randomised data. Adjuvant concurrent chemoradiation has been investigated in a number of phase two trials in patients with stage Ⅱ and Ⅲ disease and although the approach appears safe, a clear survival benefit has not been demonstrated[11,66,67]. Some clinicians are also concerned this approach might compromise the ability to deliver the recommended doses and cycles of chemotherapy. Adjuvant concurrent chemoradiation after complete surgery is therefore not considered a standard treatment, although it is currently recommended as an option after surgical resection in patients with N2 disease and positive margins in the current National Comprehensive Cancer Network (NCCN) guidelines[68].

Until further data becomes available, PORT should only be considered for patients with completely resected stage ⅢA-N2 disease, or those at high risk of local recurrence due to close/involved surgical margins.

It should not be offered to patients with completely resected N0 or N1 disease outside a clinical trial.

ONGOING STUDIES

The presence of an activating EGFR mutation has been found to be a strong predictor of a response to EGFR inhibitors[31]. In the setting of advanced NSCLC, several randomised trials have now consistently shown that patients with EGFR-mutant tumours have high response rates to front-line EGFR inhibition compared to chemotherapy[33,69,70]. Hence, despite the negative result for adjuvant gefitinib in unselected NSCLC patients in the BR19 study[30] there is enthusiasm to re-evaluate adjuvant EGFR inhibition in a patient population selected for sensitivity to this treatment. In this context the RADIANT trial compares adjuvant erlotinib with placebo in patients with EGFR-expressing tumours, and has now completed accrual[71]. Two large ongoing trials are comparing adjuvant gefitinib with chemotherapy in China[72] and Japan.

Bevacizumab, the monoclonal antibody against vascular endothelial growth factor (VEGF), has been shown to have activity in advanced NSCLC when added to chemotherapy[73,74]. ECOG has recently completed accrual into a randomised trial that examines the benefit of adding bevacizumab to cisplatin-based chemotherapy in the adjuvant setting[57].

The Tailored Post-Surgical Therapy in Early Stage NSCLC (TASTE) trial[43] examines whether customising adjuvant treatment using biomarkers will improve outcomes. Patients in the experimental arm are firstly tested for the presence of an activating EGFR mutation; patients with these mutations will receive erlotinib for 12 mo. Patients without the mutation will be further tested for ERCC1 overexpression; if this is detected they will not be given any adjuvant treatment. Remaining patients in this arm will receive chemotherapy with 4 cycles of cisplatin and pemetrexed, similarly to all patients randomised to the control arm.

Another pharmacogenomics-driven study is the International Tailored Chemotherapy Adjuvant (ITACA) trial[75]. Patients in the experimental arm are treated according to tumour ERCC1 and thymidylate synthase (TS) expression; increased expression of the latter enzyme correlates with resistance to antifolate drugs such as pemetrexed[76,77]. Chemotherapy in this arm is with cisplatin/pemetrexed (low ERCC1, low TS), cisplatin/gemcitabine (low ERCC1, high TS), pemetrexed (high ERCC1, low TS), or paclitaxel (high ERCC1, high TS). In the control group, patient/oncologist preference is used to determine which one of 3 possible cisplatin combinations will be administered.

The MAGE-A3 protein has been recently identified as a relatively "pure" tumour antigen, being otherwise expressed primarily during embryogenesis. In adult humans, only the testis and placenta express this antigen. A randomised phase Ⅱ trial of a vaccine to this antigen recruited NSCLC patients whose tumours expressed the MAGE-A3 gene[78]. There was a non-statistically significant improvement in DFS; consequently a confirmatory phase Ⅲ trial[79] has now completed accrual.

A small Japanese adjuvant study of 103 patients examined the addition of autologous activated killer T cells and dendritic cells to chemotherapy and found a statistically significant improvement in two-year survival (93.4% *vs* 66%) as well as five-year survival (81.4% *vs* 48.3%) with the addition of immunotherapy[80]. This very encouraging initial result using a novel approach will no doubt spur interest for similar studies in the future.

CONCLUSION

The survival benefit from adjuvant chemotherapy has been seen to slowly but steadily improve over the last few decades. It is now evident that cisplatin-based chemotherapy offers an absolute overall survival benefit in the order of 5% to 10%. Given that the 2 trials that have shown the highest survival benefit used 4 cycles of high-dose cisplatin in conjunction with vinorelbine, this would currently be considered the optimal treatment regimen. Whilst there is clear evidence of benefit from chemotherapy for patients with stages Ⅱ and Ⅲ disease; the benefit for stage Ⅰ tumours remains controversial. The development of a number of gene expression profile signatures to further stratify patients into low or high risk categories following conventional clinicopathological staging, may allow clinicians to determine which patients will gain a likely benefit from adjuvant therapy in the future. However this strategy requires prospective validation in randomised clinical trials. Given that the presence of activating mutations of EGFR have been found to be strongly predictive of a response to EGFR inhibitors in the setting of advanced NSCLC, similar results are eagerly awaited in the adjuvant setting. Progress in improving the survival of patients with NSCLC has been slow, but the recent improved understanding of the different molecular subtypes of this malignancy as well as the availability of new biological agents to target pathogenic pathways will hopefully translate into ongoing meaningful increments in outcome.

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