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Adjuvant chemotherapy for non-small cell lung cancer: a New Zealand perspective

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Abstract

This article reviews recent developments with the use of adjuvant chemotherapy for resected early-stage non-small cell lung cancer (NSCLC) and the implications of these developments for healthcare in New Zealand (NZ).

Non-small cell lung cancer is a major cause of mortality and morbidity in NZ, and is greatly over-represented among Māori and socioeconomically deprived populations. Early-stage NSCLC is potentially curable by surgery, but long-term outcome after surgical resection is limited by disease recurrence locally or at sites distant from the primary disease. Three recent large randomised controlled phase III trials using modern platinum-based combination chemotherapy protocols have shown significant survival benefits for the use of postoperative adjuvant chemotherapy after resection of early-stage NSCLC. Cisplatin plus vinorelbine was used as the adjuvant chemotherapy regimen in two of these trials resulting in improvements in 5-year survival of 51.2% versus 42.6% (p=0.013) and 69% versus 54% (p=0.03), respectively. In NZ, adjuvant chemotherapy for NSCLC is expected to prevent up to 15 lung cancer deaths each year for relatively low drug expenditure and has the potential to benefit Māori and the economically-deprived disproportionately more than other populations.

In conclusion, it is the opinion of this group of NZ lung cancer specialists that adjuvant chemotherapy with cisplatin plus vinorelbine should now be adopted as a standard of care for patients with resected stage II and III NSCLC. For this to occur, current PHARMAC policies preventing its use for these eligible patients will need to be revised.

Lung cancer is a major cause of mortality and morbidity in New Zealand (NZ), being the third most common cancer affecting males and the fourth most common cancer for females (Table 1).[1] In terms of cancer mortality, lung cancer is the leading cause of cancer death for males and the third most common cause of cancer death for females.

Table 1. Lung cancer incidence and mortality in New Zealand: trends and future projections[1]

Number of cases in males				Mortality		
Age	**1996**	**2011 (CI)**	**Change (%)**	**1997**	**2012 (CI)**	**Change (%)**
15+	1002	858 (618–246)	-14	881	807 (579–996)	-8
Number of cases in females				**Mortality**		
Age	**1996**	**2011 (CI)**	**Change %**	**1997**	**2012 (CI)**	**Change %**
15+	582	826 (544–229)	42	528	863 (653–100)	63

Compared to non-Māori,[1] the incidence and mortality rates of lung cancer are two to three times higher among Māori males, and more than three to four times higher among Māori females.

While lung cancer mortality rates are forecast to decrease modestly in males over the next 15 years, in females it is forecast to increase substantially due to changing trends in smoking habits in the recent decades. Indeed, these forecasts imply that by 2011/2012 lung cancer will be the leading cause of cancer deaths among females and the second leading cause of cancer deaths among males in NZ—reflecting similar trends elsewhere in the world.

Smoking cessation remains the cornerstone for preventing lung cancer and reducing the mortality and morbidity associated with this disease. However, even if current smoking rates were immediately reduced, lung cancer would remain a major clinical problem in NZ for at least the next two decades. So, efforts are also needed to improve the outcome for the many patients who will develop this disease in the coming years.

Non-small cell lung cancer (NSCLC) accounts for about 80% of all lung cancer and, when detected early, is potentially curable by surgical resection. The surgical management of early stage NSCLC includes lobectomy for the most localised disease or pneumonectomy for proximal tumours or tumours crossing interlobar fissures.

Long-term outcome of patients after surgical resection is limited by disease recurrence locally or at sites distant from the primary disease. Approximately 50% of patients with stage IB, 70% with stage II, and 80% with stage IIIA NSCLC will experience recurrence of their disease ultimately leading to cancer death despite potentially curative surgery.[2] Expected 5-year survival and local and distant recurrence rates following surgical resection of early stage NSCLC is summarised in Table 2.

Table 2. Expected outcome following complete surgical resection in NSCLC[2]

Surgical stage	5-year survival (%)	Local relapse (%)	Distant relapse (%)
IA T1N0M0	67	10	15
IB T2N0M0	57	10	30
IIA T1N1M0	55		
IIB T2N1M0	39	12	40
IIB T3N0M0	38		
IIIA T3N1M0	25	15	60
IIIA T1-3N2M0	23		

AJCC staging[18]:

T1: A tumour that is 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, and without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus)*

T2: A tumour with any of the following features of size or extent: More than 3 cm in greatest dimension; Involves the main bronchus, 2 cm or more distal to the carina
Invades the visceral pleura; Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T3: A tumour of any size that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, mediastinal pleura, parietal pericardium; or tumour in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumour
N2: Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3: Metastasis to contralateral mediastinal, contra lateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

One approach to reducing disease recurrence and cancer death following surgical resection of early stage NSCLC is to give chemotherapy postoperatively, which is a treatment approach commonly known as 'adjuvant chemotherapy'. Postoperative adjuvant chemotherapy aims to improve the cure rates achieved with surgery by eradicating distant or local micro-metastatic disease persisting after surgery that could subsequently lead to disease recurrence and cancer death. Such residual microscopic disease cannot be detected clinically but is expected to be more sensitive to chemotherapy and easier to eradicate than clinically detectable macroscopic disease.

Postoperative adjuvant chemotherapy has been a standard of care for many years for early stage breast cancer and colorectal cancer and is estimated to have prevented millions of deaths worldwide from these cancers. This article will review recent developments with the use of adjuvant chemotherapy for early-stage NSCLC and the implications these advances have for clinical practice for NZ.

Brief history of adjuvant chemotherapy for NSCLC

Adjuvant chemotherapy for NSCLC has been under clinical investigation for over 20 years. However, it is only since 2004 that positive studies have been reported and that evidence has become available that support adopting this treatment as a standard of care. Although the research completed prior to 2004 was largely negative in terms of patient outcome, a number of important findings were made that formed the basis for the developments made subsequently.

For example, the early studies identified chemotherapy agents and combination treatment protocols that had efficacy for patients with recently resected NSCLC. An important landmark was a meta-analysis of early chemotherapy trials reported in 1995 that established cisplatin as one of the most important agents for NSCLC.[3]

Part of this meta-analysis evaluated trials that compared cisplatin-based adjuvant chemotherapy with no treatment after complete resection of NSCLC. This showed an absolute improvement in 5-year survival by 5% in favour of chemotherapy treatment but this difference in survival did not reach conventional levels of statistical significance ($p=0.08$). In addition, Japanese trials of adjuvant oral UFT (Uracil-Tegafur, an oral 5-FU derivative) had shown a survival benefit in resected NSCLC but there are no confirmatory data from other countries.[4,5] At the time, this evidence was not considered to be sufficiently compelling to cause a change in clinical practice but it prompted further investigations, particularly of cisplatin-based adjuvant chemotherapy regimens in early-stage NSCLC as described in the following section.

In these early trials, some treatments were found to have a detrimental effect on patient survival, or to be associated with other clinical limitations. The use of alkylating agents such as cyclophosphamide and mitomycin C was shown to worsen survival overall in the 1995 meta-analysis of early trials of these agents in NSCLC.[3] Other chemotherapy agents and combination treatment protocols were associated with excessive toxicity, early treatment-related mortality, or poor compliance that limited their clinical efficacy. In addition, use of postoperative mediastinal radiotherapy appeared to be detrimental for the survival of some sub-groups of patients with resected NSCLC.[6]

Current trials are attempting to address the issue of which patients should receive postoperative mediastinal radiotherapy. Overall, these negative findings were important in terms of treatments that were unlikely to have clinical efficacy being abandoned.

While developments in chemotherapy protocols for resected NSCLC were occurring, advances were also being made with supportive care of patients receiving chemotherapy, and in the development of chemotherapy regimens for advanced NSCLC or for other tumour types. Improvements in the management of chemotherapy toxicities made adjuvant chemotherapy more acceptable to patients and improved their compliance with treatment. For example, the availability of serotonin type 3 receptor antagonists for the management of chemotherapy-associated nausea and vomiting was particularly important for reducing the toxicity of cisplatin.[7]

More efficacious combination chemotherapy protocols were identified in trials in advanced NSCLC. The combination of platinum-based drug with a vinca alkaloid[8] or taxane[9]became established as a standard of care for patients with advanced NSCLC and a good performance status. Compared to older combination chemotherapy protocols, these newer treatment regimens improved 1-year survival of patients with advanced NSCLC (from 15% to 30%).[8,9] These modern combination chemotherapy protocols and supportive care practices were then tested in the setting of adjuvant chemotherapy for resected NSCLC in a series of randomised trials that are described in the following section.

Recent positive phase III adjuvant chemotherapy trials in NSCLC

Three large randomised phase III trials using modern platinum-based combination chemotherapy protocols have shown significant survival benefits for the use of adjuvant chemotherapy in resected NSCLC. Cisplatin plus vinorelbine combination was used as the adjuvant regimen in two of these studies and in 26.8% of patients in the third study.[10–12] Results and dosages are summarised in Table 3. Patients with disease stages I to III were included in two studies,[10,12] and stages IB and II (excluding T3N0) in the third study.[11]

In the two studies which used cisplatin vinorelbine as the adjuvant regimen, 5-year survival was 51.2% versus 42.6 % (p=0.013) and 69% versus 54 %(p=0.03) respectively.[10,11] with a reduction in risk of death of 21% and 31% respectively.

The third study which is the largest adjuvant chemotherapy trial in NSCLC with a total of 1867 patients[12] out of which 932 patients were assigned to the chemotherapy arm had 26.8% receiving cisplatin and vinorelbine. In this study, the 5-year survival

was 44.5% versus 40.4% (p≤0.03) and a reduction of 14% in the risk of death (HR=0.86; 95% CI: 0.76–0.98).

Table 3. Positive randomised controlled trials of postoperative adjuvant cisplatin-based chemotherapy versus observation in patients with completely resected NSCLC

Study	Patients	Stage	Chemotherapy	Benefit	P value
ANITA	840	1B,11,111A	Vinorelbine 30mg/m^2 weekly × 16/20 + cisplatin 100 mg/m^2 D1,D29,D57,D65	8.6% @ 5 years	0.013
JBR 10	482	1B,11 not T3 N0	Cisplatin 50 mg/m^2 D1 & 8 q 4 weekly + vinorelbine 25 mg/m2 weekly for 16 weeks	15% @ 5 years	0.03
IALT	1867	1,11 or 111	Cisplatin 80–120 mg/m^2 Q 3weekly + etoposide 100 mg/m^2 D1-3 (56.5% of patients) or vinorelbine 30 mg/m^2 weekly(26.8% of patients) or vinblastine 4 mg/m^2 weekly ×5 then 2 weekly (11% of patients) or vindesine 3 mg/m^2 weekly ×5 then every 2 weeks (5.8% of patients)	4.1% @ 5 years	<0.03

The median relapse-free survival was also significantly better in patients who received chemotherapy in all three trials. In the ANITA trial which was recently published in Lancet Oncology, the median relapse-free survival in intention to treat population is 36.3 months in the chemotherapy arm versus 20.7 months in the observation arm (p=0.002).

In the JBR 10 trial (with a median follow-up of 5.1 years) the median recurrence-free survival was 46.7 months in the observation group and had not been reached in the chemotherapy group. The 5-year recurrence-free survival rates were 61% in the cisplatin-vinorelbine arm and 49% in the observation arm (p≤0.001).

In the IALT trial the median disease-free survival with chemotherapy was 40.2 months versus 30.5 months (p≤0.003) with no chemotherapy, and the 5-year disease-free survival rates was also significantly higher for the chemotherapy group: 39.4% versus 34.3% (p≤0.003).

Chemotherapy was not excessively toxic in all the above trials. Compliance with chemotherapy was typical for any adjuvant chemotherapy trials for lung cancer, which was reasonably good.

Median percentages of planned dose were 56.3% for vinorelbine and 76.1% for cisplatin in the ANITA trial; 58% of patients completed three cycles and 48% completed four cycles of chemotherapy in the JBR 10 trial. In the IALT trial, 73.8% of patients in the chemotherapy arm received at least 240 mg of cisplatin per square meter of body surface area.

Two patients (0.8%) died of treatment-related toxicity in the JBR 10 trial (1.7% in ANITA and 0.8% in IALT). The most common treatment-related toxicity was haematological toxicity; 12.5% of patients had febrile neutropenia in the ANITA trial, and 23% of patients had grade 3-4 neutropenia in the IALT trial (44% in the JBR 10 trial).

Further supporting evidence for the use of cisplatin-based adjuvant chemotherapy for patient with resected stage II and III NSCLC comes from a recent "Lung Adjuvant Cisplatin Evaluation (LACE)" meta-analysis of five large randomised trials including 4584 patients that was presented at 2006 ASCO annual meeting.[13] Individual patient data were collected and pooled from five adjuvant cisplatin-based chemotherapy trials (ALPI[14], ANITA[10], BLT[15], IALT[12], and JBR10[11]) conducted after the 1995 meta-analysis.

With a median follow-up of 5 years, the overall HR of death was 0.89 (95% CI: 0.82–0.96, p≤0.005) corresponding to a 5-year absolute benefit of 4.2% with chemotherapy. The benefit varied with stage and was greatest in stages II and III with a HR of 0.83 (0.73–0.95) supporting the use of cisplatin-based adjuvant chemotherapy for resected stage II and III NSCLC.

Some patients in IALT and ANITA trial received postoperative radiotherapy but those in the JBR 10 trial did not. Currently, it is uncertain whether postoperative radiotherapy should be given as well as adjuvant chemotherapy. Patients with stage IB disease did not seem to benefit from adjuvant chemotherapy in subgroup analyses of the ANITA and JBR 10 trial. In addition, the CALGB trial 9633,[16] which included only stage IB patients and used adjuvant chemotherapy with paclitaxel and carboplatin, was recently reported as being negative.

At present, the evidence does not support the use of adjuvant chemotherapy for resected stage IB NSCLC or paclitaxel plus carboplatin in the place of cisplatin plus vinorelbine.

Implications for New Zealand

This new clinical trial information discussed above relating to benefits of adjuvant chemotherapy for patients with resected NSCLC has several important implications for oncology practice and healthcare policies in NZ. Cisplatin plus vinorelbine has been adopted as an evidence-based standard of care for resected stage II and III NSCLC in many countries since these clinical trial data became available. However, in NZ this treatment is currently unavailable to eligible patients because of Pharmaceutical Management Agency (PHARMAC) restrictions preventing the use of vinorelbine for early-stage lung cancer.

There is now an urgent need to address the availability of vinorelbine for this group of patients in order to prevent lung cancer deaths and to address a major NZ health inequity. Lung cancer is currently a major cause of death in NZ and is forecast to continue to be so for several decades. The disease is greatly over-represented among the economically-deprived and Māori populations with age-adjusted incidence and mortality rates of lung cancer being two to four times higher among Māori than non-Māori, and greater than two times higher among the economically-deprived compared to well-off New Zealanders.

Adjuvant chemotherapy for NSCLC has the potential to disproportionately benefit Māori and socioeconomically-deprived populations because of their greater burden of morbidity and mortality from lung cancer relative to other NZ populations.

Until cisplatin plus vinorelbine becomes available for eligible patients with surgically resected stage II and III NSCLC, there will continue to be unnecessary and preventable lung cancer deaths in NZ. Approximately 194 patients underwent a

complete surgical resection for NSCLC in NZ in 2004 according to our recent informal survey of cardiothoracic surgical units. We estimate that approximately 100 patients will be eligible for adjuvant chemotherapy for resected stage II or III NSCLC in NZ each year, because some of the 194 patients having surgical resections will have stage I disease or for other reasons will be unsuitable for chemotherapy.

If 100 patients per year were treated with adjuvant chemotherapy then this would be reasonably expected to prevent between 4 to 15 deaths per annum given that the absolute 5-year survival benefit (range 4.1 to 15%) demonstrated in the clinical trials discussed above. So, until this adjuvant chemotherapy becomes available there may be up to 4 to 15 unnecessary and preventable lung cancer deaths in NZ each year.

An important issue for consideration is the cost of providing cisplatin plus vinorelbine treatment for patients with completely resected stage II and III NSCLC. While the costs of cisplatin and vinorelbine are well defined, they have not prevented these agents being available to oncology patients in NZ with advanced stage non-small cell lung cancer and other types of malignancy, such as breast cancer.

Given the current price of cisplatin ($117/100 mg) and vinorelbine ($560/50 mg),[17] standard doses of cisplatin (100mg/m^2 for 4 doses) and vinorelbine (25mg/m^2 for 16 doses), and an average body surface area for adults (1.8 m^2), then the total drug costs for one patient to complete a course of adjuvant chemotherapy for resected NSCLC is NZ$8900.

If 100 patients are treated each year, then the total national per annum drug bill for this treatment will be $890,000 dollars. Thus, it seems likely that with an expenditure of less than 1 million dollars per annum, adjuvant chemotherapy could be made available to all eligible patients with resected NSCLC, and this would result in the prevention of between 4 to 15 lung cancer deaths each year. But because these drug costs are soon expected to fall, the cost-benefit of cisplatin plus vinorelbine will shortly become even more favourable.

Conclusion

In conclusion, it is the opinion of this group of NZ lung cancer specialists that adjuvant chemotherapy with cisplatin plus vinorelbine should now be adopted as a standard of care for patients with resected stage II and III NSCLC. But for this to occur, current PHARMAC policies preventing its use for these eligible patients will need to be revised.

Conflict of interest statement: The authors have no potential conflicts of interests such as work for (or funding from) manufacturers of cisplatin.

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