Welcome to this review of the 4th Australian Lung Cancer Conference (ALCC) held recently in Adelaide, Australia. The ALCC is hosted by the Australian Lung Foundation, with the aim of providing a forum to raise and discuss issues relating to translating advances into clinical practice in a multidisciplinary team environment, for non-small cell lung cancer, small cell lung cancer and mesothelioma. Leading national and international lung cancer clinicians and researchers contributed significantly to the scientific programme.

Selection and review of the programme has been carried out independently by Dr Chris Lewis, a respiratory physician at Auckland Hospital.

We hope you find this Conference Review stimulating and we look forward to your feedback.

Kind regards
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Erlotinib: the Auckland experience

Presenter: Fraser A

Summary: This retrospective audit set out to review the Auckland experience of using erlotinib for advanced NSCLC patients, and to evaluate total drug acquisition costs when used as per PHARMAC guidelines. A total of 42 patients were identified from ADHB records as having commenced erlotinib between October 2010 and December 31st 2011. Patients were followed until January 31st 2012. Application for funding renewal was the surrogate marker of tumour response. A total of 20 patients (48%) were deemed responders, 14 (33%) were non responders, and 8 (19%) were classified as others (treatment failure). Total days of treatment was 5126 and total drug acquisition cost was $701,900.00; mean drug acquisition cost was $17,775. Two patients had a “response” of more than 365 days. Grade 3/4 AEs were reported in 28% of patients; serious AEs occurred in 12%, with one reported death related to treatment toxicity. In conclusion, since the introduction of PHARMAC funding for erlotinib, patients with advanced NSCLC have had greater access to targeted therapy, previously financially unattainable. The side-effect profile for erlotinib in this review was acceptable. EGFR testing is a validated predictive tool for response to EGFR TKIs. We recommend testing should be incorporated into the funding model to deliver more cost-effective, directed health care.

Comment: This audit from the Auckland regional oncology unit neatly summed up the situation with targeted therapy in New Zealand: messy. This study would initially suggest a higher response rate for erlotinib as second-line treatment than that described in the literature. However, there are two potential issues. Firstly, the definition of response in this study was the patient fulfilling PHARMAC criteria for renewal after the initial period on therapy, and this is clearly a less rigid or accurate definition than that utilized in research trials. Secondly, there is a suspicion that, whilst erlotinib is funded second line for all NSCLC in NZ, oncologists may be selecting those whom they perceive may be more likely to respond. This study does suggest that the strategy NZ is now moving toward – testing for EGFR mutations followed by funding first-line TKIs in those testing positive – will be both more clinically and more cost effective. The EGFR testing strategy, as examined by the National Health Committee, will be critical but unfortunately NHC involvement has not yet led to a uniform test, testing and funding strategy across NZ, with funding for TKIs made available by PHARMAC prior to this being resolved.

Independent commentary by Dr Chris Lewis.

Dr Chris Lewis is a respiratory physician at Auckland City Hospital. He has a clinical and research interest in lung cancer, including in particular early diagnosis of lung cancer, endobronchial ultrasound (EBUS) and interventional bronchoscopy. He is chair of the lung tumour stream of the Northern Cancer Network, and a member of the NZ MOH lung cancer work group.

For more information about the ALCC 2012, go to www.alcc.net.au/
The Queensland Lung Cancer Screening Study: risk stratification using participant data and lung function tests can significantly increase screening effectiveness.

Presenter: Marshall H

Summary: Although screening with low-dose computed tomography (LDCT) reduces lung cancer (LC) mortality in participants aged 55–74 with ≥30 pack year smoking history, it is associated with a high level of “positive” scans requiring further evaluation (25–50%) and a low rate of detection (1–2%). This study explored the potential of risk modelling with lung function and patient variables to improve the positive predictive value of screening. Participants received up to 3 annual LDCT scans. Lung function data were collected at entry. Risk stratification was determined retrospectively using a published model based on PLCO Trial data (age, socioeconomic status, positive family history, body mass index, COPD diagnosis, chest x-ray within last 3 years, smoking history). Lung function thresholds were determined by ROC analysis (% predicted FEV1 and KCO; FEV1*KCO product). A total of 256 participants were followed for a median of 30 months. Ten LC were detected (1565 LC per 100,000 patient-years; 3.9% yield). Using a model combining thresholds of 5-year LC risk ≥2% and FEV1*KCO product ≤0.85, only 129 participants would have needed to be screened in order to detect all 10 cancers, improving the potential yield to 7.8%. In conclusion, lung cancer screening efficiency can be enhanced using easily obtainable patient and physiological data. These findings need validation in larger cohorts.

Screening and early detection

Presenter: Lam S

Summary: The randomised National Lung Screening Trial (NLST) in the US found a significant 20% reduction in lung cancer mortality and a 7% reduction in all-cause mortality with LDCT compared with chest x-ray in smokers 55–74 years of age. The potential benefits of screening must be balanced against possible harms. Screening of low-risk individuals will have a low probability of benefit, and risk of causing net harm from overdiagnosis and downstream investigations or therapeutic intervention for suspicious pulmonary lesions that turn out to be nonmalignant. Two major developments may reduce downstream investigations or therapeutic intervention for suspicious pulmonary lesions:

- One is a web-based or iPad-based lung cancer risk prediction tool to identify high-risk individuals to be screened. The prediction tool was found to be accurate in the Pan-Canadian Early Detection of Lung Cancer Study. The second is a new, highly accurate lung nodule malignancy risk calculator that may reduce the number of patients requiring further evaluation (25–50%) and a low rate of detection (1–2%). This study explored the potential of risk modelling with lung function and patient variables to improve the positive predictive value of screening. Participants received up to 3 annual LDCT scans. Lung function data were collected at entry. Risk stratification was determined retrospectively using a published model based on PLCO Trial data (age, socioeconomic status, positive family history, body mass index, COPD diagnosis, chest x-ray within last 3 years, smoking history). Lung function thresholds were determined by ROC analysis (% predicted FEV1 and KCO; FEV1*KCO product). A total of 256 participants were followed for a median of 30 months. Ten LC were detected (1565 LC per 100,000 patient-years; 3.9% yield). Using a model combining thresholds of 5-year LC risk ≥2% and FEV1*KCO product ≤0.85, only 129 participants would have needed to be screened in order to detect all 10 cancers, improving the potential yield to 7.8%. In conclusion, lung cancer screening efficiency can be enhanced using easily obtainable patient and physiological data. These findings need validation in larger cohorts.

Barriers to the early diagnosis and management of lung cancer and description of best practice solutions.

Presenter: Lewis C

Summary: The pathway from presentation with lung cancer-related symptoms to diagnosis for New Zealand lung cancer patients was mapped, and barriers to prompt diagnosis explored. To achieve this, the authors undertook: (i) a literature review; (ii) an audit of patients presenting with lung cancer in 2008; (iii) interviews with patients presenting to secondary care via primary care; (iv) a survey and focus groups of general practitioners; and (v) a survey of primary and secondary care lung cancer services. Compared with an audit in 2004, the 2008 audit found that more patients were discussed at multidisciplinary meetings (56% vs. 28%), but otherwise the findings were similar. While 76% of patients presented to primary care initially, 44% of them were subsequently admitted or self-presented acutely to hospital. Although patients presenting to secondary care directly had more advanced disease, they were diagnosed quicker. Patient-related and system delays were seen in 11% and 10%, respectively. Lung cancer initiatives in New Zealand were commendable but patchy according to the findings of the secondary services stocktake. Patient and GP interviews and focus groups identified perceived problems, including fatalistic attitudes, system barriers and poor or delayed access to investigations.

A national approach to lung cancer control

Presenter: Zorbas H

Summary: Cancer Australia was established in 2006 to provide leadership in cancer control and improve outcomes for all Australians affected by cancer, their families and carers. Cancer is the leading cause of death worldwide and increases in cancer prevalence are inevitable. Lung cancer was the fourth most common cancer diagnosed and the leading cause of cancer death in Australia in 2007. Lung cancer prognosis is poor, and patients experience a high rate of distress associated with their diagnosis compared with other tumour sites. Unfortunately, we are not seeing the same improvements in outcomes for lung cancer that we are seeing with other cancers, and there is further disparity in lung cancer outcomes across population groups.

Lung cancer will continue to have ongoing and significant impacts both globally and within Australia. Much more needs to be done to provide real benefit to those most affected. National co-ordination and collaboration that can effectively address the barriers to diagnosis and care and promote the enablers of best-practice care is required. Cancer Australia is leading a 4-year (2009–2013) Australian Government commitment of $6.6 million. A review of evidence and national consultation with consumers, experts and health professionals helped set priorities for a significant body of work covering 15 projects. The current focus is upon building the evidence base, strengthening data quality and uptake of best-practice cancer care.

Comment: This large HRC study led by Dr Wendy Stevens and conducted in northern NZ has lead to a large number of recommendations to improve lung cancer care – reports available at www.northerncancer network.org.nz. It was very interesting to hear the outcomes of a similar process conducted by Cancer Australia, presented by Prof. Helen Zorbas. Many of the outcomes were strikingly similar to the NZ study, which in my view strengthens the validity of both processes. Areas identified by Cancer Australia include updating of national standards (standards published for the first time in NZ in 2011), definition of a lung cancer dataset for universal data collection (in progress), and identification of the need for upskilling of primary care physicians with the development of clear guidelines for referral for investigation and secondary care. Other overlaps included identifying the need to better inform the community of lung cancer symptoms and risks, developing an optimal model of care for lung cancer and identifying priority areas for research.

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Treatment of the elderly with lung cancer

Presenter: Singhal N

Summary: Two out of three new diagnoses of lung cancer occur in patients aged >65 years, and approximately one out of three will be aged >75 years. In the last decade, the incidence and mortality from lung cancer has decreased among individuals aged <50 years, but has increased among those aged ≥70 years. Clinical trials and practice often use chronological rather than biological age to make treatment decisions. Age 70 years is the most appropriate cutoff for clinical trials, but good clinical practice mandates geriatric assessment and determination of biological age and assessment of comorbidities to make appropriate treatment decisions. Comprehensive geriatric assessment can identify current health problems and can guide interventions to reduce adverse outcomes and to optimise individual status. The SGOD and NCCN guidelines recommend that a geriatric assessment be used to help select the best cancer treatment for an older patient with cancer. Nongeriatricians can make use of abbreviated geriatric assessment questionnaires or screening tools, like VES-13, G-8 or the Adelaide tool, to determine the functional and psychosocial status and assess the impact of comorbidities. There is strong evidence to suggest that appropriately selected older lung cancer patients tolerate and benefit from various oncological interventions like surgery, radiation and chemotherapy. Large phase III trials and meta-analyses have established the survival benefit of adjuvant chemotherapy. Large phase III trials and meta-analyses on oncological interventions like surgery, radiation and chemotherapy have established the survival benefit of adjuvant chemotherapy. Large phase III trials and meta-analyses have established the survival benefit of adjuvant chemotherapy.

Comment: This presentation was thought-provoking and relevant to daily practice, given that many patients presenting with newly diagnosed lung cancer are elderly. Clinical trials have often used age-defined cut-offs as exclusion criteria, and these tend to be translated into clinical practice and have cancer multi-disciplinary meetings. This presentation outlined the need to try to assess an individual patient’s biological age, and also to use gerontology assessments to quantify the importance of any comorbidities present. Intervention by an elderly medicine team or specialist may also help to optimize an elderly patient’s functional status, and thus allow optimum treatment to be given. The place of such assessments and intervention in lung cancer treatment has not been totally evaluated or correlated with outcomes as yet, however.

Lung cancer in indigenous Australians

Presenter: Karanth N

Summary: Indigenous Australians (Aborigines and Torres Strait Islanders) constitute only 2.5% of the Australian population. However, the population distribution is not uniform, with significantly larger proportions of people living in remote and very remote locations where access to various health-related services is scarce or difficult to reach. This has serious implications for the outcome of cancer in general, including lung cancer. A recent literature review highlighted the following five domains as major reasons for the disparity of uptake of health services: i) concerns for toxicity; ii) disconnect with physicians; iii) fears associated with ‘absence from home’; iv) different beliefs; and v) biomedical treatment failing to address holistic health. Overall, indigenous people have higher age-standardised incidence and mortality rates for lung cancer compared with the general Australian population, which are likely due to a high smoking prevalence and treatment disparity for diagnosed cases, respectively. Newer approaches are needed to reduce this gap, along with active involvement of the indigenous community.

Comment: Lung cancer outcomes for Maori and Pacific patients are known to be poorer than those of other ethnicities, as outlined in Dr Wendy Stevens’ audits. This presentation painted an even bleaker picture for outcomes in indigenous Australians. Reasons for the discrepancy in outcomes between ethnicities share some similarities, and much of the difference in mortality can be explained by lower rates of anti-cancer treatments in the indigenous population. This is in part explained by the presence of important comorbidities, with COPD and diabetes being twice as common in indigenous Australians, in addition to other problematic diseases such as strongyloides, meliodosis and latent TB. Other issues highlighted share many common features with NZ, including different and more “holistic” indigenous health models. It was good to see highlighting of the importance of engagement of indigenous populations in finding healthcare solutions.

Radiotherapy for mesothelioma: time to call it a day?

Presenter: Senan S

Summary: There is limited high-level evidence supporting a role for radiotherapy (RT) in the treatment of malignant pleural mesothelioma. Palliative RT to sites of symptomatic chest wall masses can be beneficial, although responses may be of short duration. Prophylactic RT to incision sites has been evaluated in small clinical trials, often with inconclusive results. Prophylactic chest wall irradiation is not recommended in the updated European guidelines of the ERS/ESTS and ESMO. More controversial is the role of hemithorax RT following surgery. Uncontrolled single-institution experiences from North American centres had suggested that this approach was promising. Following two prospective European trials (MAPS and EORTC), postoperative RT is no longer performed routinely in most countries as few patients appear able to tolerate the rigorous sequence of chemotherapy, surgery and large-field RT. ERS/ESTS guidelines recommend that radical surgery (EPP) should only be performed in clinical trials and at specialised centres as part of multimodality protocols [Scherpereel A, et al. Eur Respir J 2010;35(3):479–95]. In addition, postoperative RT was not advised after pleurectomy or decortication. The challenge for radiation oncologists is to identify pressing and clinically relevant research questions, and to design prospective clinical trials to address the above. Such trials should not detract from efforts to better understand the biology of this difficult-to-treat disease, or to identify more effective systemic agents.

Radiation ‘pneumonectomy’ for locally advanced malignant pleural mesothelioma: acceptable locoregional control and toxicity outcomes

Presenter: Feigen M

Summary: In this presentation, data were presented from 50 patients aged 45–75 years (84% male) with mesothelioma localised to one hemithorax treated with RT 45–60Gy over 6 weeks utilising 18F-FDG PET/CT scans to outline tumour volumes; 58% and 80% had right and epithelioid mesotheliomas, respectively, and 76% had stage III/IV disease. None of the patients had a prior extrapleural pneumonectomy, 30 underwent pleurectomy/decortication, 18 a pleurodesis and only two had a biopsy. Thirty-three patients had prior chemotherapy, including 5 trimodality cases, 17 received 3D-conformal RT and 33 had received intensity-modulated RT, which was administered to the complete hemithorax in 31 patients. Post-RT follow-up was 2–90 months (median 9.4), with 58 PET/CT scans assessed within 3–87 months. Eight patients experienced recurrence within the planning target volume, all of whom had concurrent metastases in nonirradiated sites. Recurrence only outside the planning target volume was seen in 30 patients. There were no significant acute or late toxicities and no grade ≥3 radiation pneumonitis in the absence of disease spread to the contralateral lung.

Comment: This session gave two fascinating but opposing views of radical radiotherapy for mesothelioma. The first presentation by Senan pointed out that initial promising results from single centre case series of radical RT following surgery were not confirmed by two randomized trials, which suggested that toxicity was very high. The second presentation (Feigen) was a single institution series of high-dose ipsilateral hemithoracic irradiation in patients who had mostly had a palliative rather than radical surgical procedure. It is always hard to interpret the results of such studies which lack a control group or even a nominal comparative group; in particular, it is hard to address the theoretical concern that patients may have had similar outcomes without the radiation treatment. It seems clear that, where feasible, entry into randomized studies is still appropriate for patients with this disease, which still has limited proven treatment options.
Anaplastic lymphoma kinase (ALK) rearrangement in lung adenocarcinomas – a large multicentre study of FISH and IHC

Presenter: Selinger Cl

Summary: The study presented assessed the clinical utility of ALK translocation screening and identified the frequency and clinicopathological features of lung adenocarcinomas harbouring ALK translocations using IHC and fluorescence in situ hybridisation (FISH). FISH identified ALK rearrangements in 5 of 661 samples of NSCLC tissue obtained from patients. All 5 ALK-positive cases were identified by the 5A4 ALK antibody (sensitivity 100%), and two false negatives resulted from the ALK-1 antibody (sensitivity 60%).

Comment: ALK is an uncommon but important mutation in non-small cell lung cancer. It tends to affect younger, light or non-smokers with adenocarcinoma. There is now an ALK inhibitor available – crizotinib—which has shown promising results in trials to date as second-line therapy. This study examined the important issue of appropriate testing strategies. Two are available – FISH (fluorescence in-situ hybridisation) and IHC (immunohistochemistry). The former is more expensive but considered the “gold standard”, with excellent sensitivity and specificity. Concern remains with the latter: whilst cheaper, it may have impaired sensitivity with a few “false negatives”. These would be important in a rare mutation affecting younger, light or non-smoking patients, in whom an ALK inhibitor may have a much greater impact than standard chemotherapy. This study suggests that some IHC techniques may be more reliable than others.

Frequency and spectrum of epidermal growth factor receptor (EGFR) mutations in lung cancer in an Australian testing program

Presenter: Solomon B

Summary: This presentation reported on a programme initiated in October 2010 to collect data on activating EGFR mutations in Australian patients with lung cancer. There were 337 tumour DNA samples with mutations from exons 18-21, with a total of 359 mutations out of a total of 1727 samples sequenced. Exon 19 deletions were seen in 8.9%, L858R point mutations in 5.6% and other activating mutations were seen in 8.9%, L858R point mutations in 5.6% and other activating mutations were seen in 8.9%, L858R point mutations in 5.6% and the highest prevalence. The NZ Maori and Polynesian populations have not these “real-life” samples contained insufficient material for evaluation.

Comment: This data was also presented at the TSANZ meeting in Canberra. It presents a very useful “real-life” snapshot of firstly EGFR mutation rates not planned).

The complex relationship between lung tumor volume and survival in patients with non-small cell lung cancer treated by definitive radiotherapy: a prospective, observational prognostic factor study of the Trans-Tasman Radiation Oncology Group (TROG 99.05)

Presenter: Ball D

Summary: The findings of a prospective, observational prognostic factor study of the Trans-Tasman Radiation Oncology Group (TROG 99.05) were presented. The study enrolled 509 patients with pathologically proven stage I–III NSCLC with planned RT ≥50Gy in 20 fractions using CT-based contouring. The respective 4-year survival rates according to tumour volume quartiles (lowest to highest) were 22%, 14%, 15% and 21%. A significant association was seen between larger primary tumour volume and shorter survival (hazard ratio per doubling of volume 1.06 [95% CI 1.01–1.12; p=0.029]), but statistical significance was lost after adjusting for the effects of T and N stage (1.029 [0.96–1.10; p=0.39]). However, there was evidence of an association between larger primary tumour volume and increased mortality, independent of T and N stage, over the first 18 months, but not thereafter.

Comment: This study follows up on the previous observation that there is limited correlation between tumour size and disease stage at presentation in patients with NSCLC. This prospective study suggests that tumour volume alone should not be used to exclude patients from curative attempt radiotherapy. Presumably the excess mortality seen in the first 18 months after treatment, but not beyond, might relate to toxicity from radiotherapy to a large area rather than the malignancy itself. It will be interesting to see these results published in full, and also the ease of transition into routine practice – at a clinical level it often seems to me that patients with large tumours are excluded from radical radiotherapy due to the technical or practical difficulty of irradiating large volumes, rather than because of a perceived poorer prognosis.

Novel therapies and targets in NSCLC

Presenter: Jönne P

Summary: Data on treating BRAF-mutant and KRAS-mutant NSCLC were presented. BRAF mutations are common in a variety of cancers and are detected in ~2% of NSCLCs. BRAF inhibitors are successful therapies for melanoma, but it is not clear whether they will also be effective in NSCLC, and this therapeutic approach is currently being evaluated in an ongoing clinical trial. In contrast, KRAS-mutant NSCLC is the largest genomically defined subset of NSCLC, but one for which there are few effective therapies. Approaches to treating KRAS-mutant NSCLC and data from the recent clinical trial of selumetinib and docetaxel were discussed.

Comment: There were a number of very interesting issues addressed in this excellent talk. Firstly, the importance of the molecular context was discussed in determining the significance of a mutation in lung cancer. This was demonstrated for BRAF mutations, which occur in a small number of non-small cell lung cancers, and for which inhibitors have shown utility in melanoma but it is not clear whether they will also be effective in NSCLC, and this therapeutic approach is currently being evaluated in an ongoing clinical trial. In contrast, KRAS-mutant NSCLC is the largest genomically defined subset of NSCLC, but for which there are few effective therapies. Approaches to treating KRAS-mutant NSCLC and data from the recent clinical trial of selumetinib and docetaxel were discussed.

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