Lung Cancer RESEARCH REVIEW™

Making Education Easy

Issue 15 – 2020

In this issue:

Abbreviations used in this issue

ALK = anaplastic lymphoma kinase
CT = computerised tomography
ECOG = Eastern Cooperative Oncology Group
ECOG PS = Eastern Cooperative Oncology Group Performance Status
EGFR = epidermal growth factor receptor
HR = hazard ratio
NSCLC = non-small cell lung cancer
OR = odds ratio
OS = overall survival
PD-L1 = tumour programmed death-ligand 1
PFS = progression-free survival
SCLC = small-cell lung cancer
TKI = tyrosine kinase inhibitor

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Welcome to this issue of Lung Cancer Research Review.

Investigations in this issue include a cost-effectiveness analysis evaluating the impact of low-dose CT screening for lung cancer on ethnic health inequities in NZ and clinical trials of osimertinib in resected EGFR-mutated NSCLC, pembrolizumab in patients with NSCLC and ECOG PS2, sotorasib in patients with advanced solid tumours harbouring KRAS mutation, and durvalumab plus first-line chemotherapy for mesothelioma. Other selections investigate how advances in lung-cancer treatment have affected population mortality, the influence of timeliness of first treatment on geographic variation in NSCLC mortality, and the benefits and feasibility of exercise in people with lung cancer.

We look forward to keeping you appraised of the latest developments in lung cancer research and treatment next year. In the meantime, please keep sending us your comments and suggestions.

Kind regards

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Impact of low-dose CT screening for lung cancer on ethnic health inequities in New Zealand: a cost-effectiveness analysis

Authors: McLeod M et al.

Summary: These researchers used a Markov macrosimulation model to estimate health-adjusted life-years (HALYs) and cost effectiveness of biennial national low-dose CT (LDCT) screening for lung cancer in smokers and for former smokers who had quit within the last 15 years. Changes in inequities in lung cancer survival and health-adjusted life expectancy (HALE) were also measured. The results suggest that LDCT screening in NZ is likely to be cost effective for the total population (NZ$34,400 per HALY gained) and for Māori separately. Health gains per capita for Māori females were twice that for non-Māori females and 25% greater for Māori males compared with non-Māori males. LDCT screening will narrow absolute inequities in HALE and lung cancer mortality for Māori. However, due to differential stage-specific survival, screening will increase relative inequities in mortality from lung cancer for Māori (vs non-Māori).

Comment (PD): This paper finds that a lung cancer screening programme in NZ could be cost effective in all groups and especially Māori ($27.4k per HALY gained for Māori and $36.3k for non-Māori). This is hot on the heels of a re-analysis of the previous NZ BODE group data that found cost effectiveness for Māori, but not other ethnic groups. This difference is because the current paper incudes the superior sensitivity and specificity of the radiological algorithms and risk prediction models used in the European Nelson study compared with the older NSLT models used by the BODE group. Furthermore, more realistic pricing of CT scan costs and updated predictions in stage shift also contributed to the more positive findings in this paper. These findings would support a whole population-based screening approach in NZ, but attention needs to be applied on its accessibility and acceptability to the Māori population, and on managing comorbidities in the context of radical treatment, in order that it would not have the perverse effect of widening inequity.

Reference: BMJ Open. 2020;10(9):e037145
Abstract

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Osimertinib in resected EGFR-mutated non-small-cell lung cancer

Authors: Wu Y-L et al.

Summary: To evaluate the efficacy and safety of osimertinib as adjuvant therapy, this double-blind phase III trial randomised patients with completely resected EGFR mutation-positive NSCLC to receive either osimertinib (80 mg once daily) or placebo for 3 years. A total of 339 patients received osimertinib and 343 received placebo. At 24 months, 90% of the patients with stage II to IIIA disease in the osimertinib group (95% CI: 84–93) and 44% of those in the placebo group (95% CI: 37–51) were alive and disease-free (HR for disease recurrence or death, 0.17; 99.06% CI: 0.11–0.26; p<0.001). No new safety signals were observed.

Comment (PD): At present even though osimertinib is the superior TKI as first line in previously untreated EGFR-positive NSCLC, we have been referring patients for standard chemotherapy in the adjuvant setting. This paper may be a game changer in that it shows that disease-free survival is improved using adjuvant osimertinib, but it is against placebo rather than standard therapy. An oral adjuvant treatment clearly would be much more acceptable to a patient who has recently had surgery.

Reference: N Engl J Med. 2020;383(18):1711–1723
Abstract

The effect of advances in lung-cancer treatment on population mortality

Authors: Howlader N et al.

Summary: Using data from Surveillance, Epidemiology, and End Results (SEER) areas in the US, these investigators assessed lung-cancer mortality and linked deaths from lung cancer to incident cases in SEER cancer registries. This allowed them to evaluate population-level mortality trends attributed to specific cancer subtypes and to evaluate lung-cancer incidence and survival according to subtype, sex, and calendar year. In men, incidence-based mortality from NSCLC decreased 6.3% annually from 2013 through 2016 while the incidence decreased 3.1% annually from 2008 through 2016. Corresponding lung cancer-specific survival improved from 26% in men with NSCLC that was diagnosed in 2001 to 35% among those in whom it was diagnosed in 2014. Similar patterns were noted in women with NSCLC. Contrastingly, mortality from SCLC declined almost entirely because of declining incidence, with no improvement in survival. This observation was correlated with limited treatment advances for SCLC in the time frame examined.

Comment (PD): This US registry analysis of lung cancer deaths showed that there has been an improvement in incidence related mortality and lung cancer specific survival over time. This remains the case across different genders and ethnicities. It corresponds with a reduction in incidence over time (probably reflecting decreasing smoking rates). The authors focus on improvements in treatments such as targeted therapies and immunotherapies as the main explanation. However, stage shift by screening and early detection, improved diagnostic and treatment pathways, and improved surgical techniques and ICU care may have all contributed to the improved mortality.

Reference: N Engl J Med. 2020;383(7):640–649
Abstract

Influence of timeliness and receipt of first treatment on geographic variation in non-small cell lung cancer mortality

Authors: Wah W et al.

Summary: This study evaluated the contribution of individual- and area-level risk factors on geographic variation in 2-year all-cause mortality among NSCLC patients in Victoria, Australia. Individual-level data included 3,330 NSCLC cases reported to the Victoria Lung Cancer Registry between 2011 and 2016. Area-level data included socioeconomic disadvantage, remoteness, and pollution data at the postal area level. Timely (≤14 days) first definitive treatment (OR 0.73, 95% credible interval [CrI]: 0.56–0.94) and multidisciplinary meetings (MDM) (OR 0.74, 95% CrI: 0.59–0.93) were shown to be independently associated with a lower likelihood of NSCLC 2-year all-cause mortality.

Comment (PD): The Victorian Cancer Registry has consistently been using data to drive quality improvement. Faster cancer treatment targets seem right in principle, but there has been some debate whether they make a difference to outcomes. This analysis provides evidence that shorter diagnosis to first treatment times (<14 days) is linked to better 2-year mortality outcomes. MDM discussion was also associated with better outcome, vindicating the investment in this labour-intensive resource. As well as adverse clinical factors and smoking as you would expect, social deprivation and public hospital insurance were also independently linked to mortality. Interestingly there was marked geographical variation in mortality figures even within the state of Victoria.

Reference: Int J Cancer. 2020 Oct 12. [Online ahead of print]
Abstract

Independent commentary by Dr Paul Dawkins

Paul Dawkins is a Respiratory Physician at Middlemore Hospital and Honorary Senior Lecturer in Medicine at the University of Auckland. He is clinical lead for lung cancer at Middlemore, and chairs the National Lung Cancer Working Group and Northern Cancer Network lung tumour stream. He is principal and co-investigator for a number of commercial clinical trials in respiratory medicine. He is Director of Physician Education at Middlemore Hospital and is an examiner and training workshop facilitator for RACP. He trained as an undergraduate in Bristol (UK) and then undertook postgraduate training based in West Midlands (UK), including research for a higher degree at Brigham and Women's Hospital, Boston (USA). He worked for 6 years as a respiratory physician in Wolverhampton (UK) before leaving to work in New Zealand.

Exercise for individuals with lung cancer: a systematic review and meta-analysis of adverse events, feasibility, and effectiveness

Authors: Singh B et al.

Summary: This systematic literature review and meta-analysis evaluated the safety, feasibility, and effectiveness of exercise in people with lung cancer. Thirty-two randomised controlled trials (2,109 patients) involving types of exercise interventions ranging between 1 and 20 weeks were included. No difference in the risk of an adverse event between exercise and usual care groups was found. Median recruitment rate was 59%, retention rate was 86%, and adherence rate was 80%. Significant effects of exercise compared with usual care were observed for quality of life, aerobic fitness, upper- and lower-body strength, anxiety and depression, forced expiratory volume, and sleep.

Comment (PD): This meta-analysis looked at the effect of exercise on lung cancer patients of all stages. It found that the incidence of adverse events was low and no different to usual care groups. There were positive outcomes identified across all stages and treatments and it did not depend on exercise modality. These included not just improvements in fitness and strength assessments, but also quality of life, lung function, anxiety, and sleep. It would be interesting to see how exercise regimes could be tailored to the treatment modality with prospective measurement of outcomes.

Reference: Semin Oncol Nurs. 2020;36(5): 151076
Abstract

Durvalumab with first-line chemotherapy in previously untreated malignant pleural mesothelioma (DREAM): a multicentre, single-arm, phase 2 trial with a safety run-in

Authors: Nowak AK et al.

Summary: DREAM was an Australian multicentre, single-arm, open-label, phase 2 trial designed to evaluate the activity of durvalumab given during and after first-line chemotherapy with cisplatin and pemetrexed in patients with advanced malignant pleural mesothelioma. Of 54 eligible patients who were followed up for a median of 28.2 months, 31 patients (57%; 95% CI 44–70) were alive and progression-free at 6 months. The most common grade 3–4 adverse events were neutropenia (13% of patients), nausea (11%), and anaemia (7%). A total of 60 serious adverse events occurred in 29 patients, five of which were possibly related to durvalumab. There were five deaths none of which was due to study treatment.

Comment (AL): This is only a single-arm phase 2 trial but it is heartening to see some new hope for active agents in mesothelioma. If you draw direct comparisons with the cisplatin plus pemetrexed phase 3 EMPHASICS trial the PFS benefit in DREAM is modest at best but the response rate is encouraging. The most encouraging aspect is the response in the more resistant subtypes such as sarcomatoid mesothelioma, which traditionally has a very poor outcome with chemotherapy. These results are backed up by the almost identical PrE0505 trial run in the US, which was presented at ASCO 2020 with a median PFS of 6.7 months and an immature medium OS of 20.4 months. I look forward to the phase 3 trial that is being run as a collaboration between the two groups.

Reference: Lancet Oncol. 2020;21(9):1213–1223
Abstract

Carboplatin plus etoposide versus topotecan as second-line treatment for patients with sensitive relapsed small-cell lung cancer: an open-label, multicentre, randomised, phase 3 trial

Authors: Baize N et al.

Summary: This multicentre, randomised, open-label, phase 3 trial enrolled patients (ECOG PS 0–2) with confirmed advanced stage IV or locally-relapsed SCLC, who responded to first-line platinum plus etoposide treatment, but who had disease relapse or progression ≥90 days after completion of first-line treatment. Patients were randomly assigned (1:1) to receive carboplatin plus etoposide or oral topotecan. With a median follow-up of 22.7 months, median PFS was significantly longer in the combination chemotherapy group than in the topotecan group (4.7 months, 90% CI: 3.9–5.5 vs 2.7 months, 2.3–3.2; stratified HR 0.57, 90% CI: 0.41–0.73; p=0.0041). The most frequent grade 3–4 adverse events were neutropenia (22% of patients in the topotecan group vs 14% of patients in the combination chemotherapy group), thrombocytopenia (36% vs 31%), anaemia (21% vs 25%), febrile neutropenia (11% vs 6%), and asthenia (10% vs 9%).

Comment (AL): SCLC continues to be over-represented in the NZ Māori population and remains difficult to treat. There has been little improvement in survival over the last few decades. Internationally, topotecan is the standard of care for second-line treatment of extensive disease. In the US, topotecan has been overtaken by lurbinectedin, which has shown promise in phase 2 trials but is yet to report phase 3 results. Neither of these agents are funded in NZ. Traditionally we have always felt that repeat treatment with carboplatin plus etoposide is a reasonable option. The accepted progression-free interval after first-line treatment to warrant another course varies significantly between practitioners. This trial both supports the use of repeat carboplatin plus etoposide and confirms the knowledge that the longer the interval the better the result. I would not advocate re-treatment after a 3-month interval for all of our patients but it is nice to have some solid data to back up this approach in our fittest population.

Reference: Lancet Oncol. 2020;21(9):1224–1233
Abstract

Independent commentary by Dr Aileen Ludlow

Aileen Ludlow is a medical oncologist at Auckland Public Hospital specialising in the management of Lung and GI cancer. She completed her oncology training in Christchurch before going on to do a research fellowship at the Royal Marsden Hospital in London. She is a principal and sub-investigator on several industry and collaborative group trials. She is also involved in medical oncology training, taking over as Director of Physician Education in Auckland and as a member of the NZ advanced training committee for medical oncology.

KRAS G12C inhibition with sotorasib in advanced solid tumors

Authors: Hong DS et al.

Summary: This was a phase 1 trial of sotorasib in patients with advanced solid tumours harbouring the KRAS p.G12C mutation. A total of 129 patients (59 with NSCLC, 42 with colorectal cancer, and 28 with other tumours) were enrolled. Patients had received a median of three (range 0–11) previous lines of anticancer therapies for metastatic disease. A total of 73 patients (56.6%) experienced treatment-related adverse events, including 15 patients (11.6%) who had grade 3 or 4 events. In the subgroup with NSCLC, 32.2% (19 patients) had a confirmed objective response (complete or partial response) and 88.1% (52 patients) had disease control (objective response or stable disease). The median PFS was 6.3 months (range 0.0–14.9). Grade 3–4 treatment-related toxicity occurred in 11.6% of the patients.

Comment (AL): KRAS mutations are the most common driver mutations found in lung adenocarcinoma and the G12C variant makes up the majority of them. In the past it has defied all attempts at therapeutic manipulation. Sotorasib is in the early stages of development but this phase 1 trial disease-control rate in heavily pre-treated patients is encouraging. It represents another step forward in expanding the targets for therapeutics in lung cancer. With options in development for RET fusion, NTRAK mutations, and MET amplification to name a few, the opportunities in the near future are exciting. Ultimately it is only possible to treat patients with targeted therapies if those targets can be identified. The time is coming in NZ where we need to look at next generation sequencing for all of our patients so that we can appropriately direct therapy. Given there is still disparity between DHBs around the level of testing currently offered, this needs to be addressed on a national level.

Reference: N Engl J Med. 2020;383(13):1207–1217
Abstract

Pembrolizumab in patients with non-small-cell lung cancer of performance status 2 (PePS2): a single arm, phase 2 trial

Authors: Middleton G et al.

Summary: This multicentre, single-arm, open-label, phase 2 trial evaluated the efficacy and safety of pembrolizumab 200 mg given every 3 weeks in patients with NSCLC and a rigorous ascription of PS2. In 60 evaluable patients, the incidence of durable clinical benefit (DCB; defined as the occurrence of complete response, partial response, or stable disease) was 38% (95% CI: 21–57) in first-line patients (n=24) and 36% (22–52) in subsequent-line patients (n=36). DCB incidence was 22% (11–41) in patients with a tumour proportion score (TPS) of <1% (n=27), 47% (25–70) in patients with a TPS of 1–49% (n=15), and 53% (30–75) in patients with a TPS of ≥50% (n=15). Toxicity was observed in 28% (95% CI: 19–41) of patients. No grade 5 treatment-related adverse events were observed. The most common grade 3–4 adverse events were dyspnoea (n=9), hyponatraemia (n=5), and anorexia (n=4).

Comment (AL): Unfortunately, the nature of lung cancer is that it often causes significant deterioration in a patient's health relatively quickly. By nature of its risk factors, it also occurs in tandem with other illnesses, which affect the patient's overall health. It is very common to meet patients with a new diagnosis who have an ECOG PS of 2. These are not the patients accepted into pharmaceutical industry-run randomised controlled trials. Having some data that reassure us that immunotherapy is safe and effective in patients with PS2 is immensely useful in clinical practice as it applies to a large proportion of our patients. Unfortunately, currently its use in these circumstances is still limited by the cost of the medication for the patient.

Reference: Lancet Respir Med. 2020;8(9):895–904
Abstract

Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC

Authors: Herbst RS et al.

Summary: This open-label, phase 3 trial randomised chemotherapy-naïve patients with NSCLC and PD-L1 expression (on ≥1% of tumour cells or ≥1% of tumour-infiltrating immune cells) to receive atezolizumab or chemotherapy (in a 1:1 ratio). A total of 572 patients were enrolled. The median OS was longer by 7.1 months in the atezolizumab group than in the chemotherapy group (20.2 months vs 13.1 months; HR for death, 0.59; p=0.01) in patients with EGFR and ALK wild-type tumours who had the highest expression of PD-L1 (n=205). Among patients evaluable for safety, adverse events occurred in 90.2% of those in the atezolizumab group and in 94.7% of those in the chemotherapy group. Grade 3 or 4 adverse events occurred in 30.1% of atezolizumab- and 52.5% of chemotherapy-treated patients.

Comment (AL): In many respects it is not a surprise that atezolizumab outperforms chemotherapy in treatment of PD-L1 high NSCLC. I was not especially excited or surprised to see these results. The reality of our medication funding system here in NZ means that when checkpoint inhibitors are funded for lung cancer it is unlikely that we will get a different drug for each indication. It is likely we will access one drug for all indications. More evidence that supports the idea of a class effect in lung cancer is welcome, to reassure us that substituting one for another is reasonable practice.

Reference: N Engl J Med. 2020;383(14):1328–1339
Abstract

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