Australian Lung Cancer Conference

OPTIMAL LUNG CANCER CARE *right care – right time - right place*

Day in Review

a RESEARCH REVIEW publication

16-18 October 2014, Brisbane

In today's review:

Welcome to this Day in Review for Saturday, 18th October of the Australian Lung Cancer Conference (ALCC).

The Australian Lung Cancer Conference is endorsed by the International Association for the Study of Lung Cancer (IASLC). The 2014 program is an exciting combination of science, technology, research and supportive care. The meeting is hosting 7 international experts from the specialties representing the multidisciplinary team. They are Billy W Loo Jr (Radiation Oncologist), David Carbone (Medical Oncologist), John Field (Pulmonologist), Kazuhiro Yasufuku (Thoracic Surgeon), Keith M Kerr (Consultant Pathologist), Natalie Doyle (Nurse Consultant) and Noelle O'Rourke (Clinical Consultant).

We hope you enjoy this Day in Review.

Session S1: Immunotherapeutics

Chairs: Craig Lewis and Jeff Bowden

Lung cancer immunotherapy update

Speaker: David Carbone

Summary: Professor David Carbone, Director James Thoracic Center, Ohio State University noted that we are now starting to see real progress in this area. He reviewed the process of antigen presentation, and the mechanisms by which tumours evade immune surveillance. He discussed the latest literature in relation to agents targeting PD-1, PDL-1 and CTLA-4 with reference to efficacy and toxicity, and the use of biomarkers to predict response.

Comment: The presentation by Prof Carbone focussed on the role of immunotherapy in lung cancer and on the importance of immune checkpoint inhibitors. There was discussion about CTLA-4 inhibition, but also significant presentations on the important four new PD1 and PDL-1 inhibitors. He provided detailed discussion on the results of early-phase trials of the four compounds that have entered the clinical research arena. All of the studies have clearly demonstrated benefits for these agents in patients heavily pretreated with chemotherapy. One important message that has emerged is that smokers appear more likely to respond than nonsmokers, perhaps due to various mutations in cancers of smokers. There were also suggestions that responses are: i) seen in both squamous cell carcinomas and adenocarcinomas; ii) often rapid in onset; iii) frequently prolonged in duration; and iv) sometimes apparent after the immune checkpoint inhibitor has been ceased. The other important aspect of the PD1 and PDL-1 inhibitors is that they are generally very well tolerated, with side effect profiles that are completely different to standard chemotherapy agents. There remain a number of challenges associated with these agents that need to be addressed, particularly related to the use of the PDL-1 biomarker. Responses have been seen in both PDL-1-positive and PDL-1-negative patients. The limitations of the PDL-1 biomarker include the fact that expression is dynamic and heterogeneous within tumours, and the level of expression that is important is still unclear. Trials to date have focussed on heavily pretreated patients, but are rapidly progressing to the early-phase setting, including as neoadjuvant therapy and in combinations with chemotherapy and other immune checkpoint inhibitors.

Primer on immunotherapies

Speaker: Rina Hui

Summary: Dr Rina Hui, Senior Medical Oncologist at Westmead Hospital and founding Coordinator of the Western Sydney Lung Cancer Service gave an update on what she called the basics of immunotherapy. She discussed various modalities which have potential to upregulate the immune system in order to combat cancers; cytokine therapy; anti-tumour antibodies such as trastuzumab; preventive and therapeutic vaccination; immune checkpoint inhibitors such as anti-CTLA-4, anti PD-1 and anti PDL-1 antibodies.

Comment: This session looked at immunotherapy for cancer, particularly lung cancer. This is a rapidly evolving area of research in advanced disease, and is also rapidly progressing to trials in early-stage disease. This presentation by Dr Hui focussed on the mechanisms of immunotherapy as we currently understand them.

Lung cancer vaccines

Speaker: Paul Mitchell

Summary: Associate Professor Paul Mitchell, Senior Medical Oncologist at Austin Health and Director of the North Eastern Metropolitan Integrated Cancer Service updated delegates on the most recent data for therapeutic vaccines in lung cancer. He specifically focused on three targets, the cancer-testis antigens, which are expressed in the placenta and frequently in malignancy, but only in the testis in healthy adults; the glycopeptide mucin-1 (MUC1) which is present in many malignant tissues, and the TGF-beta blocker belagenpumatucel-L.

Comment: Paul Mitchell presented on vaccines in lung cancer. While the studies thus far have been largely disappointing, there is considerable promise for combinations of vaccine therapy and other immunomodulatory therapies, particularly checkpoint inhibitors.

Radiotherapy and immunotherapy

Speaker: Catherine Bettington

Summary: Catherine Bettingon, Radiation Oncologist at the Royal Brisbane and Women's Hospital introduced the idea that radiotherapy plus immunotherapy may offer a systemic anti-tumour effect. She discussed the abscopal effect of radiotherapy, thought to be immune-mediated, and noted that radiotherapy has been shown to play a role in all stages of the immune response to a tumour, from expression of tumour antigen to priming of T-cells and cytotoxic activity by T-cells.

Expert commentary by:

Associate Professor Craig Lewis, Medical Oncologist, Prince of Wales Hospital, Sydney.

Jeff Bowden, Thoracic Physician and Head of Respiratory, Allergy and Sleep Services, Southern Adelaide Health Network.

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Session S2: New Targets

Chairs: Rina Hui and Richard Sullivan

ALTG flagship results – NITRO

Speaker: Andrew Davidson

Summary: Dr Andrew Davidson, a Medical Oncologist at Royal Perth Hospital presented interim results for the ALTG (Australian Lung Cancer Trials Group) NITRO trial. This large (n=380), multi-centre, open-label, phase III, randomised clinical trial which compared chemotherapy with chemotherapy plus nitroglycerin patch in patients with advanced NSCLC has shown negative results in the interim analysis.

Comment (RH): The presentation on the NITRO study (which turned out to be a negative study) highlighted the co-operation of different Australian cancer centres working together to recruit a huge number of participants for the study. This will help us in the future for other similar, more exciting studies. It also highlights how to look at other targets, in this case, how to deal with the tumour microenvironment, improving hypoxia. Even though the proof of principle was not confirmed, it is still important that we keep thinking of new target areas for research.

Comment (DG): The NITRO study was very impressive in that there was such extensive co-operation across Australia enabling it to be undertaken and answer its question. It was great that Andrew Davidson was very strategic in his presentation, talking about where and how this sort of co-operation should be used in the future.

New immunotherapies and antibody drug conjugates

Speaker: Ken O'Byrne

Summary: Ken O'Byrne, Professor of Medical Oncology at Princess Alexandra Hospital Brisbane presented an overview of potential new immunotherapeutic targets and their mechanisms of action. He highlighted the importance of macrophage targets such as anti CD-47 antibodies to induce macrophage phagocytosis of tumour cells and mentioned other potential new targets such as CD-96, important in natural killer cell activation. He closed by giving an update on antibody drug conjugates in lung cancer.

Comment (RH): The session on new targets highlighted the importance of translating basic science to look for new targets to further improve lung cancer treatment outcomes. We are currently in a very exciting era, with a lot of new cancer treatments becoming available, particularly targeted therapies like EGFR, TKIs and ALK fusion inhibitors. However, resistance is still a major challenge, with disease progression common after a certain period of time.

Comment (DG): It is very exciting that we have an expert such as Ken O'Byrne working in the basic science of cancer immunology in Australia. He presented some very interesting basic science approaches that may well move to the clinic soon.

Beyond TKI failure: progress in targeting ALK and EGFR in NSCLC

Speaker: Ben Solomon

Summary: Associate Professor Ben Solomon, Medical Oncologist at Peter MacCallum Cancer Centre in Melbourne, discussed the multiple and complex mechanisms by which tumours can develop resistance to first generation TKIs. Crizotinib resistance can derive from target alterations such as mutations or amplifications of the ALK gene which prevent binding. Bypass mechanisms and pharmacological failure of crizotinib in the brain may also occur. Ben also described the 2nd generation ALK inhibitors which have activity against ALK secondary mutations, in addition to being more potent inhibitors of ALK than crizotinib. Similarly resistance to EGFR TKIs arises from a mutation in EGFR kinase (T790M) in 50-60% of cases.

Comment (RH): The presentation 'Beyond TKI failure' highlighted that quite a number of new-generation targeted therapies are becoming available opening up further potential improvements in outcomes. This session also covered other new targets, including new immunotherapies, adding to a number of presentations made during the entire conference on treatments to 'release the brakes' of the immune system for fighting cancer, particularly on immune checkpoint inhibitors targeting T-cells. In this particular presentation, we heard about other targets of the immune system, including macrophages and natural killer cells. It is great to be able to co-opt all the players in the immune system and try and look into combination therapies in the future.

Comment (DG): Ben Solomon is the world expert on ALK therapies, and he gave a great talk about the approach in patients who receive targeted therapy but then relapse. He also spoke a little bit about the approach with regulatory authorities, which is an important aspect for providing access to these therapies for our patients.

Expert commentary by:

Rina Hui, Medical Oncologist Westmead Hospital, Sydney.

Dishan Gunawardana, Medical Oncologist Royal Melbourne and Western Health, Victoria.

Session S5: Looking forward

Chairs: Emily Stone and Bill Musk

Blood tests for lung cancer

Speaker: Paul De Souza

Summary: Paul de Souza, Professor of Medical Oncology at the University of Western Sydney, spoke about the reasons for looking at blood-based biomarkers in general, and the utility of circulating tumour cells (CT) and CT-DNA in particular. He outlined methods of cell harvesting and potential uses of these biomarkers including stratification of disease, detection of micrometastatic disease and resistant disease, and the ability to determine the mechanisms driving disease or resistance.

Comment: The talk by Paul De Souza on blood-based biomarkers covered the importance of proteomics and peptidomics, mRNA and circulating tumour cells for diagnosing and monitoring lung cancer. He believes they are very important for monitoring response and disease progression, and possibly, but maybe not specific, for diagnosis. They are certainly accessible and getting cheaper, but their performance characteristics need further evaluation.

Breath tests for lung cancer

Speaker: Annette Dent

Summary: Respiratory Scientist at the Department of Thoracic Medicine, Prince Charles Hospital and University of Queensland, Annette Dent presented an overview of the use of breath tests for lung cancer. Many methods are now available for detecting the different compounds exhaled in breath, although dogs, able to detect compounds at concentrations of only a few parts per trillion, may still be the gold standard method. In a 2006 study dogs distinguished lung cancer patients from healthy individuals with a sensitivity and specificity of 99%.

Comment: Annette Dent talked on exhaled breath analysis, which was "invented" by Hippocrates and popularised by Sherlock Holmes. It is very good for renal and liver failure and diabetes, but a role for diagnosing lung diseases is now emerging, especially lung cancer. It depends on volatile organic compounds (VOCs). The standard way of analysing exhaled breath has been gas chromatography, but portable, easy to use, electronic VOC detectors with the potential to be diagnostically useful have been developed.

What is new in EBUS for the management of lung cancer?

Speaker: Kazuhiro Yasufuku

Summary: Kazuhiro Yasufuku, Associate Professor of Surgery, University of Toronto and Thoracic Surgeon at the Division of Thoracic Surgery at the Toronto General Hospital gave an update of EBUS (endobronchial ultrasonography) in the management of lung cancer. He also detailed his research into lymph node characteristics which may in future aid the bronchoscopist to determine which lymph nodes, and which areas of lymph nodes contain cancer cells.

Comment: Kazuhiro Yasufuku talked about the basics of EBUS procedures, including established techniques (EBUS, transbronchial biopsy and radial probe EBUS biopsy). He then talked about various types of imaging modalities that are being developed using the newer scopes, and certain concepts of EBUS identifiable lymph node morphology, which may help predict the likelihood of node malignancy – there are many nodes visible on EBUS that cannot be biopsied. The other major development is a smaller EBUS scope, reportedly due later this year. This smaller scope may permit access to some of the less readily accessible nodes.

Surgical management of CT screening detected nodules

Speaker: Kazuhiro Yasufuku

Summary: Kazuhiro Yasufuku went on to describe use of video-assisted thoracoscopic surgery (VATS) localising techniques for peripheral lung nodules. He discussed various techniques including intraoperative imaging, percutaneous injection of liquid under CT guidance, wire coil localisation and preoperative bronchoscopic marking.

Comment: For his talk on surgical approaches to nodules detected on CT screening, Kazuhiro Yasufuku presented a case of a small peripheral nodule in a patient who was part of the PanCan dataset. A small ground-glass opacity in the lower lobe increased in solidity and size over a couple of years. CT-guided biopsy was not diagnostic. He then went on to describe the many and varied procedural options that are underway to approach such lesions. He described VATS as the procedure of choice for surgical biopsy of peripheral nodules, addressing complexities such as the inability to palpate ground glass nodules or nodules >5mm from the visceral pleura. Various options of preoperative marking of nodules were described, all of which have limitations, but are all being pursued – these include wires, fiducially and marker dyes. He then wowed the audience with a presentation on the Guided Therapeutics programme in Toronto, which includes an $8 million surgical room which looked like the Starship Enterprise and was equipped for many and varied surgical techniques, including several types of CT-guided approaches and real-time imaging. He addressed the benefits of navigational bronchoscopy and possible endobronchial approaches for coil placement. He made the point that navigational bronchoscopy really does provide excellent anatomical training for fellows, and then referred to the future potential benefit of focal ablation.

Expert commentary by:

Emily Stone, Respiratory Physician at St Vincent's Hospital, Sydney.

Professor Bill Musk, Respiratory Physician at Sir Charles Gairdner Hospital, Western Australia.

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