Immunotherapy in non-small cell lung cancer

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Abstract

Lung cancer is the leading cause of cancer related mortality and the fifth most common malignancy in Australia. Most tumours are non-small cell histology, with small cell and making up a smaller fraction of newer diagnoses. Until recently, chemotherapy was the mainstay of treatment, with relatively modest benefits seen in progression free survival and overall survival. Immune checkpoint inhibitors including pembrolizumab, nivolumab and atezolizumab are monoclonal antibodies that inhibit the association of programmed death-1 (PD-1) and it’s ligand, which is normally associated with malignancy-induced immunosuppression. There have been positive results in both the first and second line settings in metastatic NSCLC, changing the current treatment paradigm. PD-L1 testing remains a controversial predictive biomarker, used to stratify patients in several randomised phase 3 clinical trials. Current attention has shifted to combining different immune checkpoint inhibitors or in novel multi-modality combination with chemotherapy or radiotherapy. Immunotherapy has also entered into the management of stage 3 disease, and continues to be evaluated in the adjuvant and neoadjuvant settings. Toxicity remains favourable compared with conventional chemotherapy, although clinicians need to remain vigilant for rarer and severe immune related adverse events. It is an exciting time in thoracic oncology with improved and durable survival in this most lethal of malignancies.

The management of lung cancer has rapidly evolved over the last decade. There was once therapeutic nihilism in the management of advanced disease, and lung cancer chemotherapy struggled to justify a place alongside other malignancies. Platinum-based chemotherapy, with or without maintenance treatment has eventually become standard of care in those lung cancer patients without a targetable driver mutation, but this yields a median survival of approximately one year. Immune evasion is a hallmark of cancer, where an effective anti-tumour effect from the immune system is lacking. Recently, the genomic complexity and heterogeneity in non-small cell lung cancer (NSCLC) was better defined through sequencing studies. While some NSCLCs have a high mutational burden, the ability to develop a durable immune response could be predicted by the clonality of the potential neoepitope repertoire. Single oncogene driven tumours, while clonal, did not elicit a neoepitope repertoire compatible with immune checkpoint inhibition therapy. These insights help explain the limited benefit of immune checkpoint blockade for single oncogene addicted tumours, while also explaining why some patients derive prolonged remissions to such therapies.

Several studies have been performed investigating CTLA-4 inhibitors as single agents or in combination with chemotherapy. Unlike melanoma, their activity in NSCLC appears limited and ongoing studies have focused on combination approaches.

Here we explore the current data and future directions for immune checkpoint therapy in NSCLC.

First line therapy

Following on from exciting results in latter lines of therapy, immune checkpoint inhibitors have been evaluated in the first line setting. The Keynote 024 study was the first randomised phase 3 trial to show superiority of pembrolizumab over chemotherapy in the first line setting in patients with strong (>50%) PD-L1 expression. The trial screened 1653 tissue samples of which only 500 (30%) were PD-L1>50%. Of these, 305 patients were randomised to receive pembrolizumab 200mg intravenously every three weeks or platinum doublet chemotherapy. The study met its primary endpoint with a median PFS of 10.3 vs 6.0 months in favour of pembrolizumab (HR 0.50, 95% CI 0.37-0.68; p<0.001). Despite allowing for cross-over on progression, the median overall survival (OS)
is yet to be reached in the immunotherapy arm, suggesting durable responses. This has changed the sequence of therapies in NSCLC.

In contradistinction, the first line CheckMate 026 immunotherapy study comparing nivolumab with platinum doublet chemotherapy was negative. In this trial 541 patients were randomised to receive nivolumab 3mg/kg twice weekly or standard chemotherapy. Nivolumab did not demonstrate superiority for either progression free survival (PFS) or OS. This could perhaps be explained by the eligibility criteria, which set PD-L1 expression to be ≥5% rather than >50%. There was also 60% patient crossover from chemotherapy to nivolumab, and imbalances in patient characteristics including fewer patients with high PD-L1 expression in the nivolumab arm. An exploratory biomarker analysis of tumour mutational burden was undertaken in this study stratifying patients as low, medium or high depending on the number of somatic missense mutations present. A high tumour mutational burden was associated with higher response rate in the nivolumab group vs chemotherapy (47 vs 28%) and median PFS was longer (9.7 vs 5.8 months HR 0.62, 95% CI 0.38-1.00). There was no association between tumour mutational burden and PD-L1 expression, and those with PD-L1 >50% and high mutational burden had an even greater response rate (75%) than those with only one of these factors. It underlines the requirement of effective biomarkers to be paired with immunotherapeutics in an era of precision medicine.

Second line therapy

Two phase 3 trials have demonstrated nivolumab improved OS compared with chemotherapy in squamous and non-squamous NSCLC. In the CheckMate 017 trial there was an improvement in median OS 9.2 months with nivolumab (95% CI 7.3 -13.3) vs 6.0 months (95% CI 5.1 - 7.3) with docetaxel in patients with squamous NSCLC. There was doubling of response rate (20 vs 9%) and near doubling of one year survival 42 vs 24%. CheckMate 057 also demonstrated survival benefits in non-squamous NSCLC with median OS 12.2 months (95% CI 9.7-15 months) vs 9.4 months (95% CI 8.1-10.7) again when compared with docetaxel chemotherapy. Similarly there were improvements in response (19 vs 12%) and one year survival (51 vs 39%). In both these studies there were significantly lower rates of grade 3 or 4 toxicities and lower rates of discontinuation compared with the chemotherapy arm. These trials have clearly established nivolumab as a new standard of care in the second line setting in advanced squamous and non-squamous lung cancer.

Pembrolizumab also has positive phase 3 data in the second line setting with the keynote 010 trial comparing PD-1 inhibition vs docetaxel in 1034 patients with tumours ≥1% PDL-1 positive. Overall survival was superior in the subgroup with PD-L1 expression >50% receiving pembrolizumab 14.9 or 17.3 months (2mg/kg or 10mg/kg respectively) vs 8.2 months in the docetaxel arm. There were fewer grade 3-5 toxicities with pembrolizumab (13%) compared with docetaxel (34%).

PD-L1 immune checkpoint inhibitors are also effective in NSCLC with the OAK trial demonstrating benefit in the second line setting. Patients were included irrespective of PD-L1 status and 1225 patients were randomly assigned to either atezolizumab 1200mg or docetaxel every three weeks until disease progression. The pre-specified analysis of the first 850 patients met the study’s co-primary endpoint with improvement in OS in the atezolizumab 13.8 months vs docetaxel arms 9.6 months (HR 0.73 95% CI 0.62-0.87; p=0.0003). As with the nivolumab studies, benefit was irrespective of PDL-1 expression, however greater benefit was seen with tumours >50% or immune infiltrate 10% or higher for PDL-1.

Combination immunotherapy

Combining immune checkpoint inhibitors has demonstrated improved response rates and OS in patients with metastatic melanoma. Such an approach has been adopted in NSCLC with a multi-cohort phase 1 study (Checkmate 012) demonstrating promising clinical activity in chemotherapy naïve advanced NSCLC patients with a manageable toxicity profile. CheckMate 227 is a randomised open label phase 3 trial which will attempt to compare combination immunotherapy with ipilimumab and nivolumab vs nivolumab monotherapy vs platinum doublet chemotherapy in the first line setting. Combining immune checkpoint inhibitors has the potential to enhance response rates, but is tempered with a more significant immune related toxicity profile. Lessons have been learned from pivotal melanoma trials such as CheckMate 067 in melanoma with the CTLA-4 inhibitor dosing...
evolving to 1 mg/kg of ipilimumab every 6-12 weeks to maximise safety and tolerability whilst improving response.\textsuperscript{13,14}

The MYSTIC trial combination of durvalumab (PD-L1 inhibitor) with tremelimumab (CTLA-4 inhibitor) vs platinum doublet chemotherapy in first line metastatic NSCLC did not meet its primary endpoint of PFS. This was in spite of enriching the patient cohorts with ≥25% PD-L1 expression.\textsuperscript{15} The primary endpoint related to overall survival is still awaited, but other immune checkpoints may need to be targeted to improve survival.

Chemoimmunotherapy

Another approach to utilising PD-1 inhibitors is to combine with standard of care chemotherapy. The Keynote 021 cohort G open label phase 2 clinical trial explored the combination of platinum doublet chemotherapy with four cycles of carboplatin and pemetrexed followed by pemetrexed maintenance with or without pembrolizumab 200mg every three weeks.\textsuperscript{16} Cross over was allowed and patients were included irrespective of PD-L1 status. Overall response rate, the primary endpoint was favoured in the chemoimmunotherapy arm 33/60 (55%) patients responding vs 18/63 patients in the chemotherapy group (p=0.0016). PFS was also favoured with chemoimmunotherapy with a median PFS of 13 vs 8.9 months for chemotherapy (HR 0·53, 95% CI 0·31–0·91; p=0·01). These findings resulted in the FDA approving combination chemoimmunotherapy in the first line setting. Chemoimmunotherapy has the advantage of a non-overlapping toxicity profile. There are also postulated advantages of chemotherapy in terms of inducing PD-L1 expression, increasing release of tumour neo-antigens and reduction in T-regulatory cells responsible for down regulating immune response. The results of mature survival data are therefore eagerly awaited.

Immunotherapy post chemoradiation

Another novel application of immunotherapy is sequentially after radical chemoradiation in stage 3 NSCLC. The recently presented PACIFIC trial was a randomised, placebo-controlled phase 3 trial assigning patients post chemoradiotherapy to the PD-L1 inhibitor durvalumab 10mg/kg twice weekly or placebo for 12 months.\textsuperscript{17} The preplanned interim analysis of PFS was significantly longer with durvalumab 16.8 months vs 5.6 months with placebo (stratified hazard ratio for disease progression or death, 0.52; 95% CI, 0.42 to 0.65; P<0.001). The mature OS data is still awaited, and it raises further questions around the mechanisms of interaction between chemoradiation and immunotherapy.

Future directions

Immunotherapy has changed the paradigm for the management of advanced NSCLC. Unparalleled response rates, more durable than chemotherapy are being seen, giving hope to improving survival in this lethal malignancy. Attention is now shifting to other immune checkpoint targets to be exploited in combination therapies, or novel combinations with other treatment modalities such as radiotherapy. Other combinations being evaluated include PD-1 inhibition + Lymphocyte activating 3 gene (LAG3) inhibitors, as LAG3 has been noted on tumour infiltrating lymphocytes in lung cancer and is associated with poorer prognosis.\textsuperscript{18} Indoleamine 2,3-dioxygenase (IDO) has been implicated in immune evasion by tumours and represents another immune checkpoint to target.\textsuperscript{19} Epicadostat is an oral inhibitor of IDO-1 and appears safe and well tolerated when combined with PD-1 inhibitors in early phase studies and is the subject of ongoing trials.\textsuperscript{20} Finally, combining immune checkpoint inhibitors with an oncolytic virus such as CVA21 a modified coxsackie virus that specifically infects and kills ICAM overexpressing tumour cells has also signals of augmenting immunotherapy responses.\textsuperscript{21}

There is no doubt that immunotherapy is now an established treatment in the management of lung cancer. There is great cause for optimism although we must also recognise that most patients currently do not benefit from immunotherapy. However, the long term survival of some stage 4 patients treated with immunotherapy provides an important mechanistic glimpse at potentially curing advanced tumours, a phenomenon rarely witnessed with cytotoxic chemotherapy or targeted therapies. Attention needs to be focused towards smoking cessation and improved predictive biomarkers, particularly in an era of health resource utilisation.
Table 1: Completed phase 3 PD-1 pathway inhibitor NSCLC trials

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<th>Drug</th>
<th>Trial</th>
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<td>Pembrolizumab</td>
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<td>Second Line vs docetaxel</td>
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*Pembrolizumab 2mg/kg, **pembrolizumab 10mg/kg
References

15. Initial progression-free survival results from the MYSTIC trial in stage IV NSCLC. 2017: ASCO Post.