What's hot that the other lot got

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Mamta Ruparel

Lungs for Living Research Centre, UCL Respiratory, 5 University Street, London, WC1E 6JF

m.ruparel@ucl.ac.uk

1. Is risk-based selection to lung cancer screening the way forward? – Lessons from the PANCAN study

Lung cancer screening has the potential to save lives, though optimum methods for implementation in a cost-effective manner are yet to be determined. The PANCAN study (Lancet Oncol 2017;18:1523-31) was the first screening study that used a lung cancer risk prediction algorithm to determine entry into screening. This single arm prospective study recruited 2537 individuals aged 50-75 with a 2% six year risk of lung cancer as calculated by the 'PANCAN' risk prediction model, a precursor to the better performing $PLCO_{m2012}$ model. The investigators report a higher incidence of lung cancers (6.5%) compared to the National Lung Screening Trial (NLST, 4%; $p<0.001$) and a higher proportion of early stage cancers (77% of lung cancers were early stage compared with 57% in NLST and 25% in Canadian non-screening registry data, $p<0.001$). This, in combination with the low interval cancer rate (6% of total lung cancers), suggests scope for an equivalent or better mortality benefit than that reported in NLST. Another interesting finding is the low rate of cancers in patients with no nodules (n=1) compared with those with nodules >1mm (n=85). This is line with findings from NLST and the Dutch-Belgian NELSON study and supports the use of less frequent screening in individuals with no nodules on their baseline low dose CT. This study has provided compelling evidence for risk-based entry into lung cancer screening to be superior to age and smoking history alone. Such targeted screening may enhance cost-effectiveness of lung cancer screening programmes.

2. BAP1- a targetable biomarker for rTRAIL treatment of malignant mesothelioma?

To date, no agents have shown significant efficacy in the treatment of malignant mesothelioma (MM), though early in-vitro and animal studies have shown promising results with recombinant TNF-related apoptosis inducing ligand (rTRAIL). Kolluri and colleagues

(eLIFEn2018;7:e30224) report a series of experiments to identify novel therapeutic agents in MM and elucidate potential mechanisms of action to demonstrate biological plausibility of the association. In the first experiment, they treated 15 mesothelioma cell lines with 94 anti-cancer drugs and established associations between specific mutations on MM cell lines and drug response, the most significant of which was between loss of function (LOF) mutations of the tumour suppressor- BRCA associated protein-1 (BAP1) and rTRAIL. Next the investigators knocked down BAP1 expression in wild type BAP1 cell lines and showed increased response to rTRAIL compared to an empty vector. Then, by introducing either wild-type or various mutant forms of BAP1 into the cells which did not possess the BAP1 gene, they identified that BAP1 modulates TRAIL sensitivity by associating with other protein complexes in the cell. Finally, they confirmed that these findings were reproducible in further cell lines obtained from the UK Mesobank, mice models and in MM patient tumour tissue explants.

The authors have elegantly demonstrated that BAP1, LOF mutations result in modulation of specific proteins that invoke sensitivity to rTRAIL. If these findings are reproduced in human in vivo studies, BAP1 mutations could signify a biomarker for rTRAIL therapy in patients with MM.

3. Can serum LDH and full blood count determine lung cancer responsiveness to immunotherapy?

In patients with non-small-cell lung cancer (NSCLC) who express PDL-1, immune checkpoint inhibitor (IKI) treatment confers a survival advantage but currently there is a lack of a clinically accessible tool to identify patients likely to respond. Mezquita and colleagues (JAMA oncology: doi:10.1001/jamaoncol.2017.4771) used three retrospective datasets to examine the relationship between baseline plasma lactate dehydrogenase (LDH) and derived neutrophil to lymphocyte ratio (dNLR; absolute neutrophil count / [white blood cell concentration – absolute neutrophil count]) with overall survival (OS), progression free survival (PFS) and response rate (RR). They then used the data to internally and externally validate the LIPI (lung immune prognostic index) score, a composite of dNLR and LDH. In the pooled analysis of the first monocentric and second multicentric cohorts (n=466) of patients treated with IKIs, they found that median OS was 4.8 vs. 10.0 vs. 16.5 months, and median

PFS was 2.0 vs. 3.7 vs. 6.3 months (both p<0.001) for the poor, intermediate, and good LIPI groups, respectively. LIPI group also correlated with RR. The third cohort (n=162) of patients treated only with standard chemotherapy, revealed no significant differences in OS or PFS based on LIPI group and no correlation with RR. In summary, poor baseline LIPI score was correlated with poor outcomes with immunotherapy, but not chemotherapy, suggesting a potential role of LIPI as a cost effective tool to aid precision medicine in IKI treatment of NSCLC.

4. Does osimertinib improve survival in treatment naïve EGFR positive non small cell lung cancer compared with 'standard' tyrosine kinase inhibitors?

Tyrosine kinase inhibitors (TKI) have become standard therapy for patients with non-small-cell lung cancer (NSCLC) with EGFR mutations, extending survival in this patient group. However, resistance to first generation TKIs limits duration of response. The FLAURA study (NEJM 2018;378:113-25) used a phase III double blind design to compare osimertinib to standard TKIs (gefitinib or erlotinib). Participants had locally advanced or metastatic EGFR mutation positive NSCLC and were thus eligible for first line TKI treatment. The study recruited 556 participants across 132 sites in 29 countries. The primary outcome of progression free survival (PFS) was significantly longer in the osimertinib group compared with control (18.9 vs. 10.2 months, HR 0.46, 95%CI 0.37 to 0.57,p<0.001). Positive secondary outcomes included lower rate of CNS progression (6% vs. 15%); longer duration of treatment response (17.2 vs. 8.5 months); and greater decrease in lesion size (-54.7% vs. -48.5%, p=0.003). The safety profiles were similar in both groups.

The positive result seen in this meticulously executed study is likely explained by the known action of osimertinib on the common mechanism of TKI resistance, the T790M mutation. This study encouragingly suggests that osimertinib has significant clinical benefits over first generation TKIs and its use as a first line agent should further improve survival in this patient group.

References:

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