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Case Report

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Practical Application of Next-Generation Sequencing. Identification of STK11 and KEAP1 Mutations Determine Use of First-Line Chemoimmunotherapy

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Abstract

Limited targeted lung panel is the standard of care in Australia. The use of next-generation sequencing (NGS) outside major centres and clinical trials is limited. We present a case wherein a regional cancer centre NGS was obtained and identified negative prognostic somatic mutations. These mutations are not routinely investigated, but their detection consequently altered management, and most likely improved our patient's outcome.

Our patient is a septuagenarian with Stage IV, driver-negative lung adenocarcinoma, with high PD-L1 score. Standard management would warrant single-agent immunotherapy. The identification of STK11 and KEAP1 mutations through NGS alerted the clinicians of a potentially poorer response. An offer of combination chemoimmunotherapy was made which we believe has resulted in better-than-expected outcomes for this patient to date. We advocate for greater use of comprehensive molecular profiling for oncology treatment and more creative, cost-effective solutions to overcome the tyranny of distance in the practice of regional oncology.

Introduction

Primary lung cancers are the leading cause of cancer death worldwide [1]. The vast majority of lung cancers are non-small cell lung cancers (NSCLC) [2]. Most commonly, these present in the advanced stages and are unresectable at diagnosis [3].

First-line treatment depends upon the molecular biology of the cancer. Routinely tested targetable oncogenic alterations include epidermal growth factor receptor (EGFR) mutations, rearrangements in genes coding for anaplastic lymphoma kinase (ALK) and Proto-Oncogene 1, Receptor Tyrosine Kinase (ROS1) [4-6]. Determining expression of the immuno-oncological biomarker; programmed death-ligand 1 (PD-L1), is also routinely done in advanced NSCLC and results can direct treatment [7]. As more targets, such as v-Raf murine sarcoma viral oncogene homolog B (BRAF), neurotrophic tyrosine receptor kinase (NTRK), mesenchymal-epithelial transition (MET) and rearranged during transfection (RET), are discovered and matched to therapy [7,8] the need for broader panel testing becomes more apparent.

In Australia, with respect to NSCLC, Medicare Benefits Schedule (MBS)-funded tests are limited to only single gene tests for EGFR, ALK and ROS1 [4-6]. NGS, to date, is not the standard of care. Access to comprehensive molecular profiling is usually reliant upon involvement in a clinical trial or self-funding at the cost of up to $6000 AUD [9]. In the absence of any targetable genetic alterations and tumour PD-L1 expression

of ≥ 50%, pembrolizumab, a humanised monoclonal antibody against programmed death-1 (PD-1), has been approved as first line therapy in previously untreated, advanced NSCLC patients [7].Its use is associated with higher response rates than platinum-based chemotherapy [10].

Next-generation sequencing (NGS) is a high-throughput technique allowing rapid and comprehensive DNA analysis from smaller biological samples. It is recommended, where feasible, and can be employed to detect many more actionable mutations, gene fusions, and copy number variations across the genome [11,12]. In addition to detecting possible actionable mutations, NGS allows clinicians to predict a subset of patients more likely to respond poorly to immune checkpoint blockade (ICB). Serine/ threonine kinase 11 (STK11) and kelch-like ECH-associated protein 1 (KEAP1) co-mutations are common in lung adenocarcinomas (10-13%) and can be detected with NGS [13,14]. Their presence is associated with resistance to ICB and significantly worse median progression-free survival (PFS) (3.1months vs 6.3 months) and overall survival (OS) (5.8 months vs 14.5 months) with ICB when compared with patients with dual wild-type sequences [13,15-18].

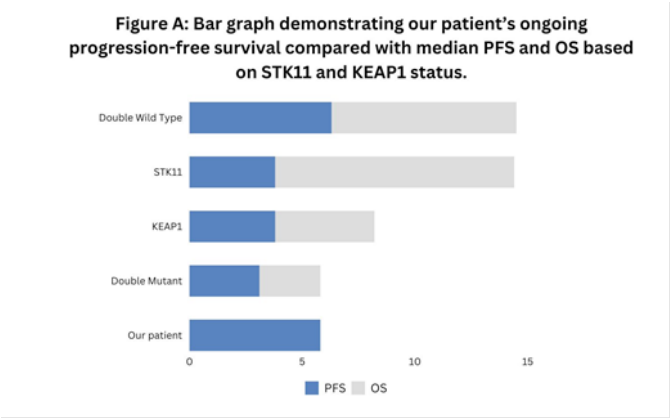

Figure A: Bar graph demonstrating our patient's ongoing progression-free survival compared with median PFS and OS based on STK11 and KEAP1 status.

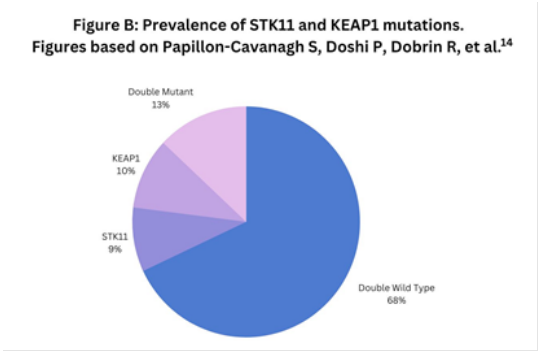

Figure B: Prevalence of STK11 and KEAP1 mutations. Figures A & B based on Papillon-Cavanagh S, Doshi P, Dobrin R, et al [14].

We report a case whereby NGS allowed the detection of STK11 and KEAP1 co-mutations in a patient with Stage IV lung adenocarcinoma with a high PD-L1 score. The molecular tumour biology informed the possibility of resistance to ICB alone; thus chemoimmunotherapy was proposed first line with excellent results ongoing.

Case Presentation

Our patient, a septuagenarian, presented with a painful mass in the left distal thigh and 5kg of weight loss. He denied any respiratory symptoms. He had a medical history of light chain monoclonal gammopathy of uncertain significance – under observation, hypertension, diverticular disease and colonic polyps. He was an ex-smoker with an 80-pack-year history.

He initially underwent an ultrasound scan and magnetic resonance imaging of his thigh mass. A core biopsy was performed and immunohistochemical profiling was consistent with poorly differentiated adenocarcinoma. EGFR, ALK and ROS1 mutations were absent. PD-L1 tumour proportion score was 70%. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) scanning confirmed an intensely FDG avid 19 x 30mm left distal thigh lesion (maximum standardized uptake value (SUV max) 19.5), 37mm PET avid left perihilar nodes (SUV max 19.3)

and a 5mm LN in the left distal thigh. Overall disease burden was low. As per guidelines first line therapy in such patients would be pembrolizumab 200mg intravenously every 3 weeks [7].

The treating clinicians in this regional Australian centre decided to access NGS via a clinical trial [19]. The presence of a K-RAS G12A mutation and coexisting KEAP1 and STK11 mutations were discovered and given the diminished efficacy of PD-1 inhibitors alone in this subgroup of patients [13-17], he was commenced on combination chemoimmunotherapy with carboplatin 5 AUC, pemetrexed 500mg/m2 and pembrolizumab 200mg IV every three weeks despite the low burden of disease.

Our patient tolerated the treatment well, with only nausea that settled with antiemetic's and Common Terminology Criteria for Adverse Events Grade 2 fatigue. Before the third cycle of treatment, he reported improvements in left thigh pain with a subjective reduction in the size of the mass. Repeat imaging at three months demonstrated nearly a 50% reduction in the size of the left perihilar mass (19mm from 37mm). Clinically the left thigh mass had resolved and was not reimaged. At 6 months repeat FDG-PET scanning demonstrated the left infrahilar mass to be 10x7mm with reduced avidity, SUV max 6.3 (previously 19.3). There was no clinically palpable thigh mass and ongoing resolution of distal thigh pain.

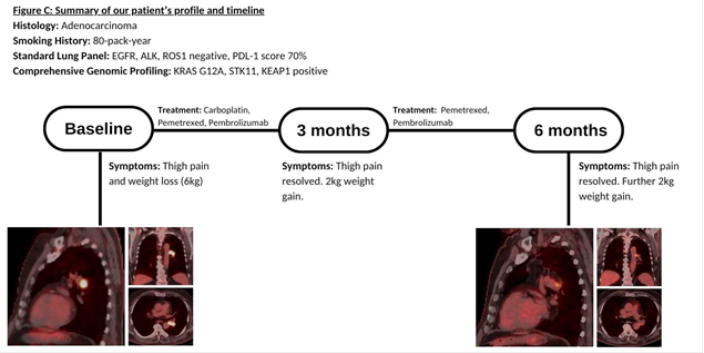

Figure C: Summary of our patient's profile and timeline.

Discussion

Although the merits of precision medicine are well appreciated, equitable access remains a challenge. Our patient presented to a regional oncology centre in Australia where routine access to NGS is almost non-existent. Barriers to wider adaptation are increasingly recognised, especially in rural and regional areas. Socioeconomic, educational and geographical factors all exacerbate the tyranny of distance in regional centres [20,21]. This requires innovative and creative solutions for regional patients in conjunction with government agencies and private enterprises.

This clinical trial, which enabled molecular profiling at no cost to the patient, required additional effort but most likely was beneficial for the patient. With recommended first line treatment, median PFS and OS in patients with STK11 and KEAP1 co-mutations are 3.1 months and 5.8 months, respectively [14]. The detection of negative prognostic co-mutations enabled open discussion with our patient. His treatment regimen recommendation subsequently deviated from the current National Comprehensive Cancer Network and Australian guidelines. Our patient's excellent partial response to chemoimmunotherapy is better than expected and remains ongoing. It has improved his quality of life and likely improved progression-free survival and overall survival. This result would have been most likely unobtainable without comprehensive molecular profiling.

The use of NGS is associated with increased identification of actionable mutations and as a result better-targeted treatment. This has led to the increased realisation of the ever-expanding universe of actionable mutations [22] and the advocating for universal NGS. Also, as in this case, the identification of co-mutation is increasingly recognised as essential when informing treatment which is only possible through upfront comprehensive molecular profiling. This, at present, is only delivered through NGS, which can be applied across a range of cancers and remains a rapidly evolving field. Results can be derived quickly and relatively cheaply [9]. We advocate for every centre to adopt NGS irrespective of the locality and challenges, not succumbing to the tyranny of distance.

Limitations

This report compares one patient's outcomes with median PFS and OS, which limits the generalizability [14]. We are unable to conclude with certainty this approach holds merits for all STK11 and KEAP1 co-mutated NSCLC on immunotherapy.

Learning Points

- Co-mutations in STK11 and KEAP1 are common in lung adenocarcinoma and are negative prognostic biomarkers. Treatment with ICB or platinum-based chemotherapy alone is generally associated with poor outcomes
- Sequencing most tumours has its merits providing an in-depth analysis of carcinogenesis drivers, potentially informing treatment and yielding better patient outcomes.
- Accessing newer technologies, clinical trials and therapeutics remain a challenge in regional Australia, necessitating innovative solutions involving multiple stakeholders.

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