Prognostic Utility of the ALI (Advanced Lung Index) in Crizotinib-Treated ALK and ROS1 Fusion-Positive NSCLC

Amanda JW Gibson[1], Michelle Dean[1], Anifat Elegbede[1], Aliyah Pabani[1,2], Gwyn Bebb[1], Winson Y. Cheung[1,2]

[1]Department of Oncology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada, [2]Tom Baker Cancer Centre, Department of Oncology, Alberta Health Services, Calgary AB, Canada,

Background

The discovery of oncogenic fusion events within the ALK and ROS1 tyrosine kinase domains, and subsequent development of precision therapies to target these oncogenic drivers have significantly improved the prognosis for patients with these types of gene rearrangements. [1] However, a proportion of patients, estimated to be in the range of 20%, [2-3] fail to demonstrate favorable response to targeted therapies with a commensurate negative impact on patient outcome. Given this reality, it is important to be able to identify patients at risk of non-response to targeted therapies; this may help reveal the mechanisms behind lack of response and identify patients for whom best supportive care may yield the best quality of life and outcome.

In this context, prognostic indices, which are non-invasive, low cost and based on peripheral blood components may be key to revealing the individual tumour microenvironment - impacted by chronic systemic inflammation - which plays a significant role in cancer development, progression and outcome, and response to systemic therapies.[4-5] Blood component based prognostic indices have shown association with outcome in NSCLC, [5] but evaluation of these indices in relation to targeted systemic therapy remains underexplored, and in contemporary clinical settings patient performance status remains the most common metric to help determine treatment suitability, given its ability to predict response. [6]

In response, this study sought to evaluate the potential of the Advanced Lung Index (ALI), a lung-specific, histology-agnostic, unified index of blood-based markers associated with systemic inflammation, as a prognostic marker of treatment response and patient outcome in ALK and ROS1 fusion-positive NSCLC treated with crizotinib.

Methods

The institutional Glans-Look Lung Cancer Research Database contains demographic, clinical, pathological, treatment and outcome data from patients diagnosed with NSCLC living in the Canadian province of Alberta. This data repository was used to identify all patients with ALK or ROS1 fusions treated with crizotinib between 2014 and 2021 in the province of Alberta, Canada.

ALI was calculated using metrics gathered from routine bloodwork taken in the 30 days preceding crizotinib therapy initiation:

$$\text{ALI} = \frac{\textit{Body Mass Index} \times \textit{Serum Albumin}}{\textit{Neutrophil:Lymphocyte Ratio}}$$

Patients were stratified by ALI score using previously established cut-off values: [7]

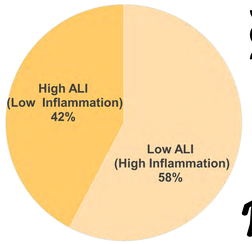
High Systemic Inflammation: Low ALI (ALI score < 18)
Low Systemic Inflammation: High ALI (ALI score ≥ 18)

Univariate and multivariate analyses were used to compare ALI groups and potential impact on outcome and response.

Results & Interpretation

59 patients were identified:

Demographic and Clinical Characteristics of Cohort



83% ALK Fusion

76% Good ECOG (<2)

20% Brain Metastasis at Crizotinib Initiation

31% Prior Non-Targeted, Palliative-Intent Systemic Therapy

61% Female

56% Never Smoker

Median age at Diagnosis: 59 years
Interquartile range: 48 – 71 years

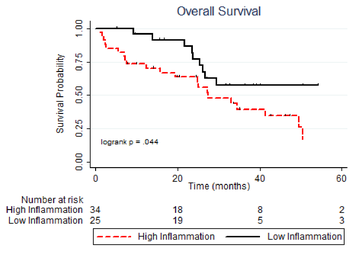
Patients in High and Low ALI groups did not differ significantly on any demographic or clinical characteristics except that those with Low ALI (compared to High ALI) were more likely to have brain metastases [32% vs. 4%, X^2, df(1), p=0.004]

ALI and Response to Crizotinib

ALI scores were significantly associated with response to crizotinib, where Low ALI scores, representing high systemic inflammation, had lower rates of positive response to crizotinib (stable disease or better), and higher rates of non-response to crizotinib

ALI Score	Response to Crizotinib		
	Objective Response Rate (ORR)	Disease Control Rate (DCR)	Non-Responder (NR)
Low ALI (n=34)	29%	62%	35%
High ALI (n=25)	60%	96%	4%
X^2 p-value	0.02	0.01	0.002

ALI and Overall Survival



Overall survival, measured from the onset of advanced or metastatic disease discovery was differed significantly by ALI score (log-rank p=0.04), and where High ALI (low systemic inflammation) were observed to have superior survival times in comparison to Low ALI (high systemic inflammation) patients.

ALI Score	mOS [95% CI]
Low ALI	27.4 months [15.7 – 14.6]
High ALI	Not reached [25.3 – Not reached]

Decreased survival time in Low ALI patients may be related to a higher rate of non-response to crizotinib (35%) thereby limiting the array of targeted options available.

Results & Interpretation

ALI and Brain Metastases

Most patients with brain metastases at crizotinib initiation also had Low ALI (96%)

In patients without brain metastases Low ALI was still significantly associated with:

Decreased overall survival:
25 months vs. Not Reached
log-rank p=0.04

Reduced Response to crizotinib:
ORR: 35% vs. 63% (p=0.05)
DCR: 61% vs. 100% (p<0.001)
NR: 35% vs. 0% (p<0.001)

ALI and ECOG

ECOG was also prognostic of patient outcome, and associated with crizotinib response, but its ability to differentiate response to crizotinib was poorer than that of ALI scores:

ALI (Low vs. High):	ECOG (Poor vs. Good)
Significant association with ORR, DCR and NR to crizotinib.	Significant association with only DCR and NR to crizotinib

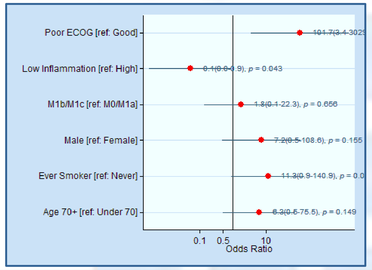
Low ALI was present in 100% of non-responders to crizotinib without brain metastases, but ECOG was only considered poor in 75% of these non-responders

Features Associated with Non-Response to Crizotinib (Multivariate)

A multivariate model, controlling for known confounders, confirms that both poor ECOG and Low ALI (high systemic inflammation) are predictive lack of response to crizotinib therapy

Poor ECOG [ref: Good]
OR: 101.7, p=0.008

High ALI [ref: Low]
OR: 0.1, p=0.04



Conclusions

- ALI scores were predictive of clinical response to crizotinib and prognostic of patient outcome in the Alberta cohort of ALK and ROS1 fusion-positive patients
- ALI scores are an inexpensive and accessible tool which can complement more subjective assessments of patient performance status.
- ALI scores may have particular value in identifying patients at risk of poor clinical response to crizotinib, particularly among those without brain metastases.

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This work was funded by a generous donation to the Glans-Look Lung Cancer Database | Glanslook.ca