9P - HLA-I homozygosity as a predictive biomarker for developing immune related adverse events (irAE) among non-small cell lung cancer (NSCLC) patients treated with single agent immunotherapy

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INTRODUCTION

- Immune checkpoint inhibitors have revolutionised the management of NSCLC.
- However, the development of irAEs is associated with morbidity that can be lifelong and even fatal.
- While it has been suggested that human leukocyte antigen (HLA-I) homozygosity is associated with worse overall survival among NSCLC treated with single agent immunotherapy[1,2], its association with toxicity has not been examined.

AIM

Explore the association between HLA-I/II homozygosity and incidence of toxicity among metastatic NSCLC patients treated with single agent anti-PD-1/PD-L1 therapy.

METHODS

- We collected blood from 193 NSCLC patients treated with anti-PD1/L1 in the first- or second-line setting.
- Blood cells DNA was extracted and high-quality HLA typing performed.
- Toxicity data was collected and graded as per common terminology criteria for adverse event (CTCAE) V5.0. Univariate analysis using GraphPad Prism was used to correlate between HLA-I/II homozygoosity with toxicity.
- We investigated the relationship between toxicity, clinical benefit rate (CBR), progression free survival (PFS) and overall survival (OS).
- In addition, we investigated the association between irAEs and different HLA-I/II supertypes and genotypes.

RESULTS

- A total of 179 patients with metastatic NSCLC were suitable to be included in the analysis. Most are male, smokers and ECOG 1 or less (Table 1).

Table 1: Patients demographic and genomic HLA status.

Patient characteristics	N (%)
Age	
≥65	107 (59.8)
<65	72 (40.2)
Sex	
M	101(56.4)
F	78 (43.6)
ECOG	
≤1	151 (84.4)
>1	26 (14.5)
Unknown	2 (1.1)
Smoking	
Yes	146 (81.6)
No	22 (12.3)
Unknown	1 (6.1)
Histopathology	
Adenocarcinoma	122 (68.2)
SCC	48 (26.8)
Others	9 (5)
Molecular status*	
KRAS mutant	61 (46.6)
KRAS wild type	56 (42.7)
KRAS unknown	14 (10.7)
EGFR, ALK or ROS1 mutant	5 (3.8)
PDL1 Status	
≥50%	77 (43.0)
1-49%	27 (15.1)
<1%	26 (14.5)
Unknown	49 (27.4)
Line of treatment	
First line	55 (30.7)
Second or more	124 (69.3)
Genomic HLA-I status	
Homozygous at one or more loci	34 (19)
Heterozygous at all loci	145 (81)
Genomic HLA-II status	
Homozygous at one or more loci	62 (34.6)
Heterozygous at all loci	117 (65.4)
Total	179

*Molecular status was only examined in NSCLC with non- squamous cell carcinoma histology (131 patients). ALK, echinoderm microtubule-associated protein like-4-anaplastic lymphoma kinase (*EML4/ALK*) fusion; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; F: female; HLA-I/II: human leukocyte antigen I/II, KRAS, Kirsten Rat Sarcoma GTPase; M: male; NSCLC, non-small cell lung cancer; PDL1: program death ligand-1; SCC: squamous cell carcinoma.

RESULTS

Relationship between genomic HLA-I/II zygosity and irAEs

- Homozygosity at one or more HLA-I loci, but not HLA-II, was associated with reduced risk of irAE (RR=0.57, P=0.025) (Table 2).
- None of the patients with homozygosity at one or more HLA-I loci developed pneumonitis of any grade (P=0.037) or grade 3 toxicity (P=0.023) (Table 2).

Table 2: Summary of observed irAEs and prevalence of homozygosity at one or more HLA-I loci among patients developed irAEs.

irAE	Any grade N (%*)	HLA-I Homozygous Frequency N (%#)	RR (95%CI)	P value	≥ Grade 3 N (%*)	HLA-I Homozygous Frequency N (%#)	P value
Any event	**103 (58)**	**9/ 78 (5.1)**	**0.57 (0.31-0.96)**	**0.025**	17 (9.5)	**0/17**	**0.023**
Skin rash	34 (19)	4/34 (11.8)	0.57 (0.22-1.38)	0.172	3 (1.7)	0/3	
Arthralgia	20 (11)	4/20 (20)	1.06 (0.41-2.40)	0.552	0		
Pneumonitis	**15 (8)**	**0/15**		**0.037**	7 (3.9)	0/7	
Endocrinopathy	12 (7)	0/12		0.073	0		
Hepatotoxicity	11 (6)	0/11		0.091	4 (2.2)	0/4	
Colitis	7 (4)	2/7 (28.6)	1.54 (0.43-3.78)	0.397	3 (1.7)	0/3	
Lethargy	3 (2)	1/3 (2.9)	1.78 (0.32-4.69)	0.471	0		
Nephritis	1 (0.5)	0/1		0.810	0		

*Comparing to all patients, 179. # Frequency of homozygosity among patients who developed specific irAE;

Relationship between HLA-I/II supertypes and alleles and irAEs

- HLA-A03 supertype was associated with increased risk of developing irAE, (RR=1.40, P=0.039) (Table 3).
- HLA-DRB1*0401 allele was associated with increased risk of developing irAE (RR=1.51, P=0.023).
- None of the patients with HLA-DQB1*0301 experienced gastrointestinal toxicity (RR=0.00, P=0.048).

Table 3: Association of HLA-I supertypes with development of any irAE

HLA-I supertype	Frequency N (%*)	RR (95%CI)	P value
A24	18 (23.1)	1.08 (0.71-1.54)	0.425
A01	30 (38.5)	0.79 (0.55-1.11)	0.117
A02	43 (55.1)	1.24 (0.89-1.75)	0.131
A03	**49 (62.8)**	**1.40 (0.99-2.01)**	**0.039**
B58	9 (11.5)	1.33 (0.76-1.94)	0.209
B62	18 (23.1)	1.23 (0.82-1.74)	0.196
B27	13 (16.7)	0.88 (0.54-1.34)	0.368
B44	39 (50)	0.81 (0.58-1.13)	0.135
B07	34 (44.7)	0.92 (0.65-1.29)	0.362
B08	17 (21.8)	0.91 (0.59-1.33)	0.389

*out of 78 patients developed toxicity

Relationship between irAEs and clinical outcome

- The occurrence of any irAE was associated with improved CBR (RR=1.94, P<0.0001), PFS (HR=0.37, P<0.0001) and OS (HR=0.26, P<0.0001).

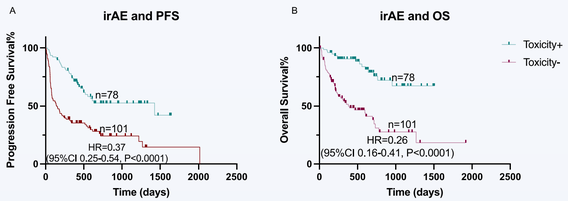

Figure 1: Correlation between irAE and clinical outcome. A) PFS, B) OS, PFS: progression free survival, OS: overall survival .

CONCLUSION

- Genomic HLA-I homozygosity can be a predictive marker for the development of irAE among NSCLC patients treated with single agent anti-PD1/PDL1 therapy.
- Further analysis of the above correlation within the different ethnic groups will give a better understanding of the role of different HLA supertypes and genotypes in different population

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First and presenting author has no conflict of interest to declare.