CHOLESTEROL HOMEOSTASIS AND IMMUNE-INFLAMMATORY PROFILES IN PATIENTS WITH mRCC RECEIVING IMMUNOTHERAPY

Pietro Tuttobene[1], Michele Maffezzoli[2], Giorgia Leali[1], Monica Pluchino[1,2], Elda Favari[3], Giulia Mazzaschi[1,2], Federica Pecci[1,2], Marcello Tiseo[1,2], Massimo Di Maio[4], Sebastiano Buti[1,2]-1 Department of Medicine and Surgery, University of Parma, Parma, Italy, 2 Medical Oncology Unit, University Hospital of Parma, Parma, Italy, 3 Department of Food and Drug, University of Parma, Parma, Italy, 4 Medical Oncology 1, AOU Città della Salute e della Scienza di Torino, Turin, Italy

Background

Cholesterol metabolism may modulate antitumor immunity, influencing response to immune-checkpoint inhibitors (ICIs). We evaluated cholesterol transport-related biomarkers, KIM-1, and inflammatory mediators in patients with metastatic renal cell carcinoma (mRCC) treated with first-line ICI-based regimens, aiming to characterize the immune–metabolic profiles.

Methods and study design

Preliminary analysis of LINCHOLM, a prospective, multicenter, observational study: 33 patients with mRCC were included.

T0: before starting ICI-based combinations.

Tissue analysis:
- Cholesterol transport biomarkers (ABCA1, ABCG1)
- Tumor immune microenvironment (TIME)
- PD-L1 expression

Blood analysis:
- Lipid profile
- Immune cell phenotyping
- Soluble biomarkers (Apo A1, Apo E, KIM 1, sPDL1, cytokine)
- ABCA1- and ABCG1-mediated cholesterol efflux (CE)

T1: after 6 weeks.

T2: at disease progression

Primary objective was to investigate the association between baseline cholesterol transporters and inflammatory mediators, and progression-free survival (PFS).

Patient population

Characteristics	Overall (n=33)
Sex	
Male	25 (75.8%)
Female	8 (24.2%)
Age	
Range	44.1 - 87.7
ECOG PS	
0 - 1	28 (84.8%)
2	5 (15.2%)
Surgery	
No	14 (42.4%)
Yes	19 (57.6%)

Characteristics	Overall (n=33)
Metastatic sites	
≤ 3	25 (75.8%)
> 3	8 (24.2%)
IMDC	
Good	5 (15.2%)
Intermedite	20 (60.6%)
Poor	8 (24.2%)
Treatment	
ICI+TKI	12 (36.4%)
ICI+ICI	21 (63.6%)

Results

Correlations between IMDC and baseline biomarkers

Across worsening IMDC risk groups Apo-A1, total cholesterol, HDL and LDL decreased, whereas KIM-1, IL-6 and Apo-E significantly increased (figure 1 and figure 2).

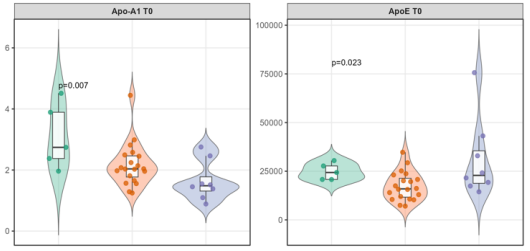

Figure 1 *Violin plots showing the distribution of Apo-A1 and Apo-E levels across IMDC risk subgroups (green: good-risk; orange: intermediate-risk ; viole: poor-risk).*

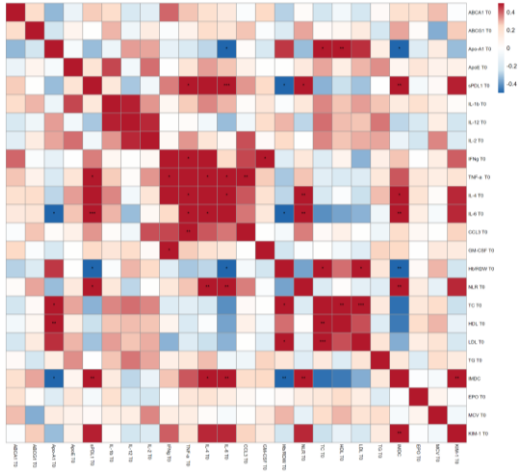

Figure 2 *Heatmap of Spearman correlation coefficients between baseline cholesterol-related parameters, circulating lipid fractions, cytokines, inflammatory indices and IMDC. Only correlations with an absolute Spearman's rho ≥ 0.5 are shown. Color scale indicates the direction and strength of the correlation. Asterisks denote statistical significance after Benjamini–Hochberg (BH) FDR correction (*FDR < 0.05, **FDR < 0.01, ***FDR < 0.001).*

Correlations between ABCG1-CE, KIM-1 and inflammatory mediators

High ABCG1-CE was associated with higher levels of ApoE, IL-1β, and increased PD-1 on CD4+ and monocite (figure 3). High KIM-1 was associated with poorer ECOG PS (p = 0.016), synchronous metastatic disease (p = 0.001), and higher NLR, IL-4, IL-6, IL-10 and sPDL1 (figure 4).

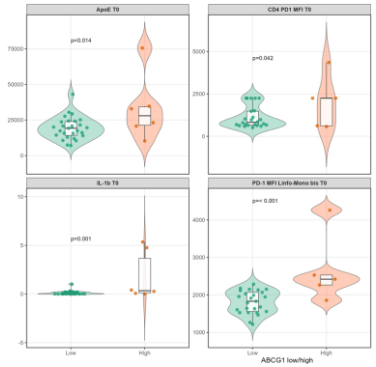

Figure 3 *Violin plots showing the distribution of baseline biomarkers across ABCG1- mediated CE groups.*

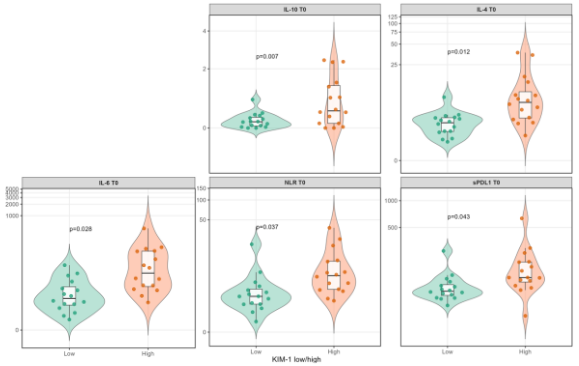

Figure 4 *Violin plots showing the distribution of baseline biomarkers across KIM-1 groups.*

Survival outcomes

High baseline ABCG1-mediated CE (p < 0.001), KIM-1 (p = 0.002), ApoE (p < 0.001), NLR (p = 0.008), and inflammatory cytokines: IL-4 (p = 0.005) , IL-6 (p = 0.009), IFN-γ (p = 0.043), IL-10 (p = 0.007), IL-1β (p = 0.002), IL-2 (p < 0.001), and TNF-α (p = 0.002) were associated with shorter PFS. Only ABCG1 remained independently associated with worse PFS at multivariable analysis (HR 10.61, 95%CI 2.35–47.97; p = 0.002), although estimates were limited by the small sample size (figure 5).

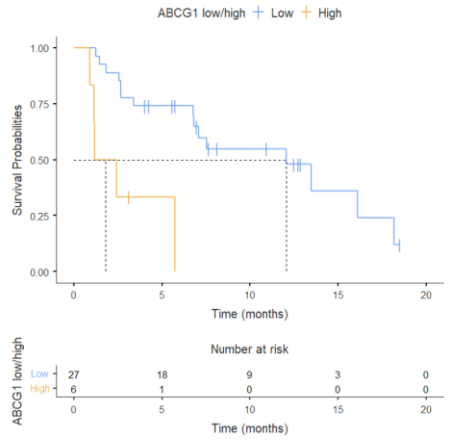

Figure 5 *Kaplan–Meier curves for PFS stratified by low vs high baseline ABCG1-mediated CE.*

Conclusion

ABCG1-mediated CE may serve as a prognostic biomarker in patients with mRCC receiving first-line ICI-based therapies. The interplay among cholesterol metabolism, KIM-1, and inflammatory mediators suggest a biological profile that may influence outcomes and warrants further validation.

Acknowledgements

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