Evaluation of CD39, CD73, and CD38 as potential biomarkers for monitoring Mogamulizumab response in Sézary Syndrome (abstract)

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Background: Sèzary Syndrome (SS) is a rare and aggressive leukemic form of cutaneous T-cell lymphoma with neoplastic CD4+ T cells (Sézary cells) in the skin, lymph nodes, and blood (1). The anti-CCR4 monoclonal antibody Mogamulizumab (Moga) has been shown to increase progression-free survival in advanced/refractory SS, though patients still ultimately progress (2). Recently, we and others demonstrated aberrant overexpression of CD39 or CD73 ectoenzymes (3,4) and low CD38 levels (5,6) on circulating and skin-homing CD4+ T-cells from selected subgroups of SS patients.

To identify novel biomarkers for monitoring SS, we investigated the expression of these ectoenzymes in circulating CD4+ and CD8+ T-cells in a cohort of SS patients treated with Moga.

Methods: Multiparametric flow cytometry was longitudinally performed on circulating CD4+ and CD8+ T cells from 12 SS patients before (baseline) and during Moga.

Results: At the baseline, we identified a subgroup of patients with remarkable high frequency of CD39+ cells among tumor cells. Genetic analysis confirmed that the CD39 levels in SS cells correlate with the rs10748643(A>G) polymorphism in the ENTPD1/CD39 gene. Specifically, patients with the GG and AG genotypes exhibited higher CD39 expression on SS cells, compared to AA individuals.

During Moga treatment, 10 out of 12 patients showed early complete or partial depletion of SS cells in the blood. This response was characterized by a rapid increase in CD38 expression in the repopulating circulating CD4+ and CD8+ T cells. Additionally, AG and GG patients (with high baseline CD39 expression) exhibited a simultaneous reduction in CD39 levels in residual CD4+ T cells. In one patient with the AA genotype, characterized by low CD39 but high CD73 expression at the baseline, the response to treatment led to a reduction in CD73 expression. On the contrary, non-responders showed no variation of the ectoenzymes on T cells.

Moreover, three responders experienced blood and/or skin disease progression. These patients were characterized by an opposite modulation of the ectoenzymes, with CD39 upregulation and CD38 downregulation on CD4+ and CD8+ T-cells.

Conclusions: The aberrant expression of CD39 and CD73 on SS highlights the potential for exploiting these ectoenzymes as markers for SS cells identification. In addition, the different modulation of these markers on repopulating cells during Moga response and disease progression provides insights into the potential role of these ectoenzymes for monitoring patients' treatment response. A more in-depth characterization of the tumor and normal T-cell subsets expressing these ectoenzymes is ongoing.

References

1. *Willemze R, Cerroni L, Kempf W, Berti E, Facchetti F, Swerdlow SH, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. Blood. 2019;133(16):1703–14.*
2. *Roelens M, de Masson A, Andrillon A, Ram-Wolff C, Biard L, Boisson M, et al. Mogamulizumab induces long-term immune restoration and reshapes tumour heterogeneity in Sézary syndrome*. Br J Dermatol. 2022;*
3. *Yakymiv Y, Marchisio S, Ortolan E, Bracci C, Senetta R, Rumore MR, et al. CD39/CD73 dysregulation and adenosine metabolism contribute to T-cell immunosuppression in patients with Sézary syndrome. Blood. 2023;141(1):111–6.*
4. *Sonigo G. Letter to Blood Involvement of the CD39 / CD73 / adenosine pathway in T-cell proliferation and NK cell-mediated antibody-dependent cell cytotoxicity in S ezary syndrome. 2022;139(17):2712–6.*
5. *Quaglino P, Novelli M, Fava P, Ortolan E, Astrua C, Tonella L, et al. CD38 Expression by Circulating and Skin-Infiltrating Lymphocytes from Sezary Syndrome Patients: A Flow Cytometry and Immunohistochemistry Study. Dis Markers. 2022;2022:1–7.*
6. *Ta VA, Battistella M, Zhao LP, Dobos G, Ram-Wolff C, Madelaine I, et al. CD38 Targeting in Aggressive, Treatment-Refractory Cutaneous T-Cell Lymphomas. J Invest Dermatol. 2023;143(7):1329-1332.e3.*

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