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O-135

SNP rs10748643 within the promoter region of ENTPD1 (the gene encoding CD39) has no prognostic value in Sézary patients

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Introduction: Sézary syndrome (SzS), an aggressive variant of Cutaneous T-cell lymphoma, has a poor prognosis and a very limited therapeutic arsenal. Many studies focused on the identification of (genetic) markers that could enable early recognition of patients at risk and reliably predict the disease course. Recently it was reported that SNPs in the promoter region of *ENTPD1* that determine expression of ectoenzyme CD39 has prognostic relevance for patients with SzS. In a cohort study using Sanger sequencing and SNP6 arrays in SzS patients it was found that patients with the A genotype (determining low CD39 levels in T-cells) have a significant worse survival compared to G subjects (higher CD39 expression levels).

Objectives: To validate these findings, this SNP was studied in an independent cohort of 62 SzS patients and retrospectively correlated with survival data to anticipate future use in a clinical setting.

Materials and methods: DNA was isolated from CD4+ T-cells from SzS patients meeting all WHO-criteria and present in our biobank (with clinical data including survival). SNP status was assessed by Sanger sequencing and copy number status of the same region was analysed by digital PCR.

Results: The *ENTPD1* region was diploid for 35 of the 62 patients (26 showed loss, 1 gain) and the observed allele frequency in diploid samples does not significantly differ from the Genome of the Netherlands (p=0.2094). Kaplan Meier analysis (comparing "A/A" vs "A/G or G/G" or "A/A" vs "A/G" vs "G/G) did not show a significant difference (p=0.934 resp. 0.379). Similarly, no significant differences were found for Kaplan Meier analysis of all samples (n=62) focusing on tumor cell genotype (comparing "A/A or A/-" vs "A/G or G/G or G/-" or "A/A or A/-" vs "A/G" vs "G/G or G/-"; p= 0.637 resp. 0.624).

Conclusion: In contrast to earlier studies, a relation between disease course of SzS patients and the rs10748643 SNP was not found. CD39 protein expression on tumor cells might still be indicative but this labor intensive and costly procedure cannot be replaced by relatively simple genetic assays at this stage. In the course of this analysis we noted that the allele frequency of the SNP in the Italian cohort studied earlier is skewed (A:0.630 vs G:0.370) and the same applied for the genotype distribution. However, this difference does not differ significantly from the normal allele frequency as compared to the European genome (p=0.057) and expected genotype distribution as compared to the Hardy Weinberg equation (p=0.251).

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The overlap of skin and blood T-cell clones in early-stage mycosis fungoides

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Introduction: Mycosis fungoides (MF) is the most common subtype of cutaneous T-cell lymphoma that starts in the skin but can progress to involve blood with significant mortality in late stages. Even in early stages and in the absence of blood involvement, changes in blood T-cell receptor (TCR) repertoire have been observed in MF. While prior work has explored the significance of dominant blood T-cell clones in the prognosis of early MF, the relationship between TCR sequences and T-cell repertoires of blood and skin in early-stage MF patients has not been characterized.

Objectives: To determine the relationship of blood and skin T-cell repertories and to reassess the impact of dominant blood T-cell clones on selected outcome endpoints in early-stage MF.

Materials and methods: We used high-throughput sequencing to interrogate TCR sequences in blood and skin of MF patients without blood involvement at the Jefferson Cutaneous Lymphoma Clinic (Adaptive Biotechnologies). ImmunoSEQ Analyzer provided T-cell repertoire overlap metric (Morisita's index) and diversity measure (Simpson's clonality score). Time to systemic treatment (TTST) was calculated as the time from initial diagnosis to initiation of first systemic therapy.

Results: 60 MF patients with no blood involvement were enrolled. 28% had a dominant clone in blood; of these, 18% were identical to dominant skin clones and 82% were distinct from the dominant clones identified in skin. We found that MF patients with discordant dominant T-cell clones in blood and skin had a longer TTST when compared to the identical clone cohort (P=0.0057). Furthermore, patients with discordant dominant clones had a lower degree of T-cell repertoire overlap between blood and skin (P<0.0001) and higher blood T-cell repertoire diversity scores (P=0.013) when compared to the identical clone group. In all patients, the degree of T-cell overlap in blood and skin did not significantly change over a period of months to years or among skin biopsies obtained from different anatomical sites. Finally, in a subset of patients with discordant clones, the dominant skin clone did not appear to be detected in blood even at low frequencies.

Conclusion: We propose that early-stage MF patients with dominant clones in blood segregate into two cohorts with distinct prognoses and T-cell repertoires based on the identity of their peripheral T-cell clones. Our findings suggest that not all MF patients have reservoirs of malignant T-cell clones readily available in peripheral circulation to seed new lesions in skin.

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Oncogenic drivers in NF-kappaB pathway-related elements provide candidate targets for future targeted therapies in Sézary syndrome

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Introduction: Sézary syndrome (SS) is a leukemic variant of CTCL showing a marked clinical and genetic heterogeneity resulting in a lack of effective target treatments. Efforts to uncover the oncogenic drivers for SS have been mainly focused on whole-genome or whole-exon sequencing (WGS or WES) results from SS patient samples. However, these strategies have some limitations since a detailed clear-cut contribution of the mutated genes to lymphomagenesis may be variable and has not been fully established.

Objectives: To further refine the list of oncogenic drivers in SS and to identify possible candidate targets for future targeted therapies.