LETTER

Use of cerebrospinal fluid CXCL10 and neopterin as biomarkers in HTLV-1-associated myelopathy/tropical spastic paraparesis treated with steroids

INTRODUCTION

Human T-cell leukaemia virus type 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis (HAM/TSP) damages the spinal cord by chronic inflammation and causes progressive lower limb motor disability.[1] Because the associated symptoms gradually progress over the years, it is challenging for clinicians to predict long-term functional prognosis and evaluate the treatment response. Recently, we proposed criteria for classifying disease activity in untreated patients.[2] As per this classification, disease activity is classified as low, moderate or high based on the clinical course and concentrations of inflammatory cytokines C-X-C motif chemokine 10 (CXCL10) and neopterin in the cerebrospinal fluid (CSF). Although corticosteroids are widely used to slow disease progression,[3] biomarkers for steroid-treated patients have not yet been validated. In the present study, we investigated whether these markers are associated with the progression of motor dysfunction in this population.

MATERIALS AND METHODS

This was a single-centre, retrospective cohort study of patients diagnosed with HAM/TSP based on the WHO criteria.[4] Patients who were continuously treated with oral prednisolone (PSL) therapy and had the following data were enrolled: CXCL10 and neopterin concentrations in the CSF measured before and after the initiation of PSL therapy and serial data of the Osame motor disability score (OMDS) (online supplementary figure S1).[5]

Patients visited St. Marianna University hospital every 1 to 3 months for treatment for HAM/TSP; motor disability was assessed using the OMDS at each visit. The PSL dose and the interval between the initiation of PSL therapy and CSF testing were not standardised. Oral PSL therapy was initiated at a median dose of 5.0 mg/day (IQR 3.0–5.0), and the dose was adjusted thereafter according to the symptoms (dose range 1.5–8.0 mg/day). The median time from the initiation of PSL therapy to CSF testing performed after the therapy initiation (post-PSL CSF test) was 6.2 months (IQR 4.4–9.5). The CXCL10 concentration was measured using a cytometric bead array (BD Biosciences, Franklin Lakes, New Jersey, USA). The neopterin level was measured using high-performance liquid chromatography at a commercial laboratory (SRL, Tokyo, Japan).

The study endpoint was defined as a 1-point increase in OMDS from the time of the post-PSL CSF test. The survival function of time to 1-point deterioration of OMDS was estimated using the Kaplan-Meier method. To evaluate associations of the biomarkers, the Cox regression model was used to estimate HRs and 95% CIs. Statistical analyses were performed using EZR software version 1.40. All p values were two sided, and statistical significance was defined as 0.05.

RESULTS

Patient characteristics

Thirty patients were enrolled in this study. The median follow-up period was 4.1 years (IQR 2.7–5.2). Patient characteristics are shown in online supplementary table S1. The concentrations of CXCL10 and neopterin were well correlated during both pre-PSL and post-PSL period (Spearman's correlation 0.80 and 0.88, respectively) (online supplementary figure S2). CXCL10 and neopterin concentrations decreased after therapy initiation (online supplementary figure S3A, B). OMDS improved in seven (23.3%) patients after a median treatment period of 2.0 months (IQR 1.0–3.8); however, OMDS in four of the seven patients worsened after initial improvement (online supplementary figure S3C). Eight of the 23 patients without initial OMDS improvement experienced worsening of OMDS during follow-up.

Association between CSF markers and OMDS deterioration

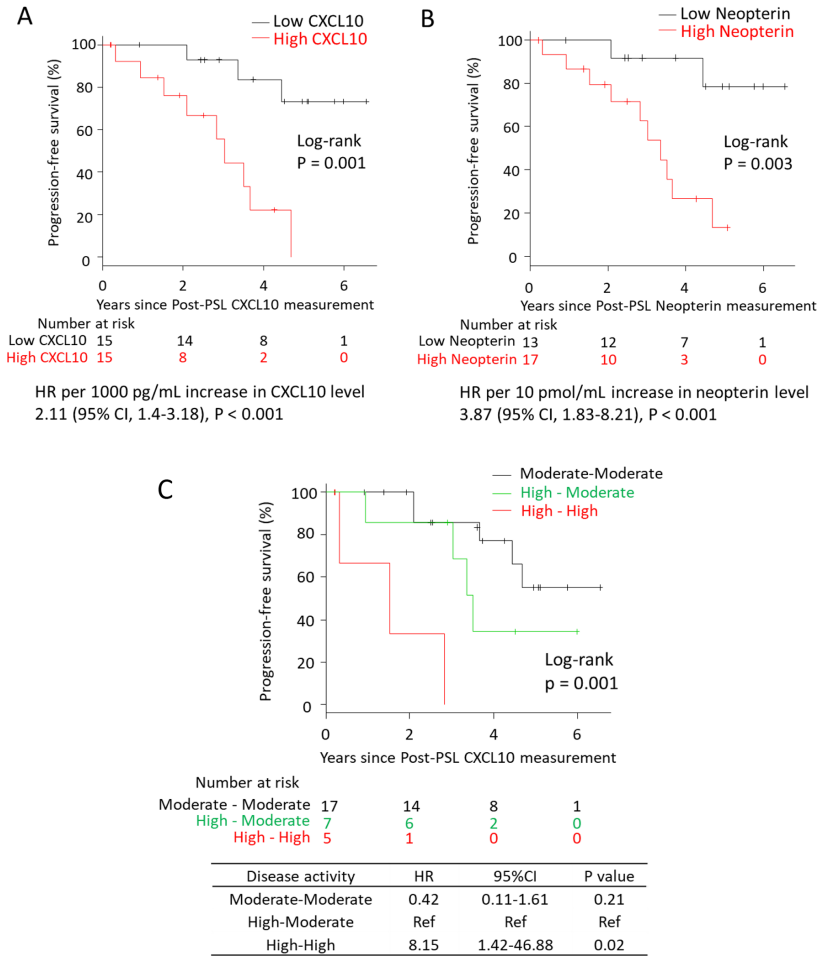
Patients were stratified into low and high post-PSL CXCL10 groups based on the median post-PSL CXCL10 levels. Characteristics of the two groups are shown in online supplementary table S2. Kaplan-Meier analysis showed a higher rate of 1-point OMDS deterioration after post-PSL CSF testing in the high CXCL10 group than in the low CXCL10 group (log-rank, p=0.001; figure 1A). HR per 1000 pg/mL increase in CXCL10 concentration for motor function deterioration was 2.11 (95% CI 1.40 to 3.18; p<0.001). The association between the post-PSL neopterin concentration and the deterioration rate was similar to that between the CXCL10 concentration and deterioration rate (HR per 10 pmol/mL increase in neopterin concentration, 3.87 (95% CI 1.83 to 8.21), p<0.001; figure 1B, online supplementary table S3).

Association between the change in CXCL10 concentration after PSL therapy and OMDS deterioration

We compared the rate of 1-point deterioration of OMDS after post-PSL CSF testing among the three groups stratified by disease activity based on the CXCL10 concentrations during both pre-PSL and post-PSL period: 17 patients with moderate activity at pre-PSL and post-PSL (moderate-moderate), 7 with high-moderate and 5 with high-high (online supplementary table S4).[2] Characteristics of the three groups are shown in online supplementary table S5. HR of moderate-moderate versus high-moderate was 0.42 (95% CI 0.11 to 1.61; p=0.21; figure 1C) and that of high-high versus high-moderate was 8.15 (95% CI 1.42 to 46.9; p=0.02), indicating that the progression was more rapid in patients whose CXCL10 concentrations remained high. Similar analyses of neopterin were not performed because there was only one patient in the high-high group.

DISCUSSION

We demonstrated that higher concentrations of CXCL10 and neopterin measured during low-dose oral PSL therapy were associated with subsequent functional deterioration, suggesting that measuring the concentration of these markers during therapy has prognostic value. We also showed that patients whose CXCL10 concentrations remained high despite treatment had a higher risk of functional deterioration. This indicates that reduction in CXCL10 concentration after PSL therapy is associated with a lower risk of functional deterioration and shows its potential as a biomarker for both treatment response and outcome. Therefore, CXCL10 measurement should help clinicians assess both disease status and treatment effect and guide treatment decision-making to improve long-term prognosis. Moreover, CXCL10 may play a role as a surrogate marker in future clinical trials because the change in its concentration after PSL treatment was associated with a change in long-term



Disease activity	HR	95%CI	P value
Moderate-Moderate	0.42	0.11-1.61	0.21
High-Moderate	Ref	Ref	Ref
High-High	8.15	1.42-46.88	0.02

Figure 1 Associations of progression rate of motor disability with CXCL10 and neopterin concentrations in the cerebrospinal fluid. Kaplan-Meier analysis to evaluate the rate of 1-point increase in OMDS from the point of the cerebrospinal fluid test performed after the initiation of prednisolone therapy. (A and B) Patients were stratified into (A) low and high CXCL10 and (B) low and high neopterin groups based on the median value (1818.2 pg/mL for CXCL10, 9.0 pmol/mL for neopterin). (C) Disease activity of HAM/TSP is stratified into three groups based on the CXCL10 concentration: low (CXCL10 <320 pg/mL), moderate (CXCL10 320–4400 pg/mL) and high activity (CXCL10 ≥4400 pg/mL).[2] Patients were stratified into three groups based on the combination of the disease activity before (pre-PSL) and after (post-PSL) the initiation of PSL therapy: moderate at pre-PSL and post-PSL (moderate-moderate), high at pre-PSL and moderate at post-PSL (high-moderate) and high at pre-PSL and post-PSL (high-high) groups (online supplementary table S4). One patient whose CXCL10 decreased from moderate to low activity and OMDS remained at 6 throughout the 3 years of follow-up was excluded from the analysis. Differences in the progression rate were tested by the log-rank test. HRs were calculated using the Cox regression model. CXCL10, C-X-C motif chemokine 10; HAM/TSP, human T-cell leukaemia virus type 1–associatedmyelopathy/tropical spastic paraparesis; OMDS, Osame motor disability score; PSL, prednisolone.

motor function. Although we did not perform this analysis on neopterin, we believe that neopterin may have similar potential because CXCL10 and neopterin concentrations were highly correlated.

In conclusion, we demonstrated that CXCL10 and neopterin are promising prognostic biomarkers for steroid-treated patients with HAM/TSP. Additionally, CXCL10 might have utility as a biomarker to monitor treatment response. Further studies with a larger sample size are necessary to determine biomarker cut-off values to better guide treatment for HAM/TSP.

Junji Yamauchi ,[1] **Tomoo Sato** ,[1] **Naoko Yagishita,**[1] **Natsumi Araya,**[1] **Daisuke Hasegawa** ,[1] **Shuntaro Tsutsumi,**[2] **Misako Nagasaka,**[2,3] **Ariella Coler-Reilly,**[2] **Eisuke Inoue** ,[4] **Ayako Takata** ,[5] **Yasuhiro Hasegawa,**[6] **Yoshihisa Yamano**[1]

[1]Department of Rare Diseases Research, Institute of Medical Science, St. Marianna University School of Medicine, Kawasaki, Japan
[2]Department of Advanced Medical Innovation, St. Marianna University Graduate School of Medicine, Kawasaki, Japan
[3]Department of Oncology, Karmanos Cancer Institute, Wayne State University, Detroit, Michigan, USA
[4]Medical Informatics, St. Marianna University School of Medicine, Kanagawa, Japan
[5]Department of Preventive Medicine, St. Marianna University School of Medicine, Kawasaki, Japan
[6]Department of Neurology, St. Marianna University School of Medicine, Kawasaki, Japan

Correspondence to Dr Yoshihisa Yamano, Department of Rare Diseases Research, Institute of Medical Science, St. Marianna University School of Medicine, Kawasaki 2168512, Japan; yyamano@marianna-u.ac.jp

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ORCID iDs
Junji Yamauchi http://orcid.org/0000-0002-6090-2183
Tomoo Sato http://orcid.org/0000-0001-8439-3128
Daisuke Hasegawa http://orcid.org/0000-0003-0292-1594
Eisuke Inoue http://orcid.org/0000-0002-1652-7769
Ayako Takata http://orcid.org/0000-0002-7792-8195

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