CXC Chemokine Receptor 3 and CC Chemokine Receptor 4 Expression in T-Cell and NK-Cell Lymphomas with Special Reference to Clinicopathological Significance for Peripheral T-Cell Lymphoma, Unspecified

Takashi Ishida, Hiroshi Inagaki, Atae Utsunomiya, Yoshifusa Takatsuka, Hirokazu Komatsu, Shinsuke Iida, Genji Takeuchi, Tadaaki Eimoto, Shigeo Nakamura, and Ryuzo Ueda

ABSTRACT

We recently reported expression of the chemokine receptors CXC chemokine receptor 3 (CXCR3) and CC chemokine receptor 4 (CCR4) in adult T-cell leukemia/lymphoma and showed a preferential expression of CCR4 and its association with an unfavorable outcome. In the present study, we extend our adult T-cell leukemia/lymphoma study to other subtypes of T- and NK-cell lymphoma, to clarify whether a characteristic chemokine receptor expression pattern is obtained for each of the subtypes defined by the WHO classification. CXCR3 and CCR4 were heterogeneously expressed in peripheral T-cell lymphomas, unspecified (PTCLU). We next focused on PTCLU and analyzed the clinical significance of the chemokine receptors and their association with FoxP3, a hallmark of immunoregulatory T (Treg) cells. Multivariate analysis showed that CCR4 expression was an independent and significant unfavorable prognostic factor ($P < 0.001$). A significant correlation was found between mRNA expression of CCR4 and FoxP3, suggesting a possible association of CCR4-positive tumors with Treg cells and thereby with an immunocompromised state. Chemokine receptors may be useful not only for further characterization of the T- and NK-cell lymphomas but also in predicting clinical outcomes for patients. We suggest that a specific therapy targeting the CCR4 molecule may be developed as an alternative treatment for patients with CCR4-positive tumors.

INTRODUCTION

Chemokines belong to a superfamily of small, cytokine-like proteins that induce cytoskeletal rearrangement, firm adhesion to endothelial cells, and directional migration of leukocytes by interacting with G-protein-coupled receptors (1–3). This leukocyte trafficking, which is critically regulated by chemokines and their receptors, shares many similarities with tumor cell migration and metastasis (4). In addition, it has generally become accepted that the expression profile of chemokine receptors in normal T-cell subsets is associated with their cytokine secretion profiles. Specifically, CXC chemokine receptor 3 (CXCR3) and CC chemokine receptor 5 (CCR5) are considered to be selective markers for the Th1 phenotype, whereas CCR4, CCR3, and CCR8 are markers for the Th2 phenotype (5–10).

The WHO classification of malignant lymphoma has successfully classified B-cell lymphomas into distinctive clinicopathological entities by evaluating a combination of clinical, immunological, and genetic features. In contrast, many of the T- and NK-cell lymphoma subtypes lack specific gene alterations and expression markers and therefore remain poorly defined. In particular, PTCLU is not one of the better defined entities, because this classification includes a heterogeneous group of T-cell neoplasms. PTCLU accounts for as many as half of the PTCL cases (11–13). In the clinical setting PTCLU is one of the most aggressive of the non-Hodgkin lymphoma subtypes. These patients respond poorly to therapy, show frequent relapses, and present with a very poor prognosis (11–15). Additional studies are needed to better characterize T-cell and NK-cell lymphomas, in particular PTCLU, and to elucidate their biological and genetic bases, to apply the most suitable treatments to individual cases.
have been reported for various T-cell lymphomas, and this may explain, in part, the distinctive patterns of spread associated with each tumor subtype (16, 17). We have reported recently that most adult T-cell leukemia/lymphoma (ATLL) cells express CCR4 and that this is associated with an unfavorable outcome (18). It is generally known that the surface phenotype of adult ATLL cells is represented by their positivity for CD4 and CD25, and these patients have frequent infectious complications (19). Recently, it was found that Treg cells exist in the CD4+CD25+ T cell population (20–23). Based on these observations, we hypothesized that ATLL cells may originate from CD4+CD25+ (CCR4+) Treg cells, and preliminarily reported that FoxP3, a hallmark of Treg cells, was highly expressed in ATLL cells (24), which may lead to the severe immunocompromised state of the patients.

We here extend our earlier ATLL study (18) to include other subtypes of T- and NK-cell lymphomas, to clarify whether a characteristic chemokine receptor expression pattern is obtained for each of the subtypes defined by the WHO classification. We performed immunohistochemical analysis on paraffin sections of Th1-associated CXCR3 and Th2-associated CCR4 expression, evaluating 169 cases of T- and NK-cell lymphomas other than ATLL. A novel mouse-human chimeric anti-CCR4 monoclonal antibody (MoAb), which may be clinically applicable to molecular target therapy, was generated recently (24, 25) from the mouse anti-CCR4 MoAb used in the present immunohistochemical analysis. Next we focused on PTCLU and analyzed the clinical and prognostic significance of CXCR3 and CCR4 expression. Furthermore, we investigated the correlation between expression levels of each of the chemokine receptors and the FoxP3 gene to clarify the underlying biology of PTCLU.

MATERIALS AND METHODS

Patient Selection. This study included 169 patients with T-cell and NK-cell lymphomas who were diagnosed between 1989 and 2003 at four independent hospitals in Japan (Nagoya City University Hospital, Imamura Bun-in Hospital, Aichi Cancer Center Hospital, and Shizuoka Saiseikai General Hospital). Clinical data analyzed in this study included age, sex, stage, presence or absence of B symptoms, extranodal tumor involvement, performance status (PS), serum lactic dehydrogenase (LDH) level, WBC count, hemoglobin (Hb) level, platelet (Plt) count of the peripheral blood, and tumor-involved organs (lymph node, bone marrow, liver, spleen, gastrointestinal tract, lung, central nervous system, and skin). All clinical data were retrieved at the time of lymphoma diagnosis. Although the treatments for T-cell and NK-cell lymphoma patients enrolled in this study varied, combination chemotherapies containing doxorubicin, such as the cyclophosphamide, vincristine, and prednisone regimen, were prescribed for most of the PTCLU patients.

Histopathology. Tissue biopsies were performed to obtain sufficient amounts of tumor materials. The patients gave informed written consent prior to the sampling procedure, and informed consent was provided according to the Declaration of Helsinki. Specimens were fixed in 10% buffered formalin and embedded in paraffin. All cases were reviewed by hematopathologists (H. I. and S. N.) and classified according to the criteria of WHO classification of malignant lymphoma after precise immunohistochemical evaluation. ATLL cases were excluded from the present study because they were analyzed extensively in our previous study. Mycosis fungoides (MF) cases with no apparent large tumor cells (MF of eruption or plaque stages) were not included in this series because it is usually difficult to identify MF tumor cells with minimal atypia admixed with many reactive lymphoid cells (26). PTCLU cases were classified histologically into four variants as follows: (a) large or medium-sized cell type, (b) small cell type, (c) Lennert variant type, and (d) T-zone variant type.

Monoclonal Antibodies against Chemokine Receptors and CD25, and Immunohistochemistry. We used mouse MoAbs against CCR4 (KM2160) and CXCR3 (1C6, BD PharMingen, San Diego, CA; ref. 5, 16, 18, 27). The KM2160 recognizes the extramembrane NH2-terminal portion (amino acids 12–29) of the CCR4 molecule. Expression of CD25 (4C9, Novocastra Laboratories Ltd., Newcastle, United Kingdom) was analyzed in 44 cases with PTCLU. Immunohistochemistry was performed with an automated immunostainer (OptiMax Plus, BioGenex, San Ramon, CA) using a SUPER SENSITIVE MultiLink detection kit (BioGenex). We defined a specimen as positive for CXCR3, CCR4, or CD25 when >10% of the tumor cells were stained with the respective antibodies.

Real-Time PCR for CCR4, CXCR3, and FoxP3 of the Affected Lymph Node Cells. When the affected lymph node biopsies were performed, the specimens were disaggregated into a single cell suspension in RPMI 1640, and the viable cell fraction was obtained using ficoll-paque (Pharmacia, Uppsala, Sweden). The samples were then washed twice in PBS and cryopreserved with RPMI 1640 containing 10% heat-inactivated fetal bovine serum and 10% DMSO (Wako, Osaka, Japan) at −130°C. The patients gave informed written consent prior to the sampling procedure, and informed consent was provided according to the Declaration of Helsinki. We analyzed these samples from ten PTCLU patients, which consisted of >50% of the apparent lymphoma cells microscopically, and total RNA samples were prepared from them. After incubation with DNase I, the RNA was reverse transcribed to first-strand cDNA using an oligodeoxythymidylic acid primer. The aliquots of cDNA solutions were used to quantify CCR4, CXCR3, FoxP3, and β-actin mRNA. CCR4 and CXCR3 were PCR-amplified with primer sets purchased from Roche Molecular Biochemicals (Mannheim, Germany), according to the manufacturer’s instructions. FoxP3 was amplified with the following exon-spanning primers: sense, 5′-GAGGACTTCTCAGAGCAT-3′ and antisense, 5′-TGCATGGCACTAGCTCTT-3′. PCR was carried out in a 20-μl reaction mixture containing 2 μl of serially diluted cDNA, 2 μl of FastStart DNA master SYBR Green I (Roche Molecular Biochemicals), and 0.5 μmol/L of each primer with the aid of a LightCycler Quick System 330 (Roche Molecular Biochemicals). β-Actin was used as an internal control (this primer set was purchased from Roche Molecular Biochemicals). The standard curve for each gene was generated by amplifying serially diluted plasmids incorporating cDNA of the individual genes, and these were used to determine the absolute copy-number of target gene expression. Quantitative assessment of the mRNA of interest was performed by dividing its expression level by that of β-actin and was expressed as a
copy-number ratio. All assays were conducted in triplicate, and the mean value was reported as the mRNA level. Consequently, a CCR4 copy-number ratio of 1 was defined as $4.48 \times 10^{-4}$ copies of CCR4 mRNA per β-actin mRNA. A CXCR3 copy-number ratio of 1 was defined as $5.65 \times 10^{-5}$ copies of CXCR3 mRNA per β-actin mRNA.

**Fig. 1** Immunohistochemical expression of CXCR3 and CCR4 in T- and NK-cell lymphomas. A, AILT; tumor cells show prominent expression of CXCR3 while they are negative for CCR4. B, ALK+ALCL; the large anaplastic tumor cells are positively stained for CCR4, whereas CXCR3 are detected in some background reactive small lymphocytes. C, MF in transformation; the large tumor cells are negative for CXCR3 and positive for CCR4. Some small lymphocytes are stained for CXCR3. D, PTCCLU; the majority of tumor cells are positive for CCR4 but negative for CXCR3 (H&E).

### Table 1 Expression of CCR4 and CXCR3 in T-cell and NK-cell neoplasms

<table>
<thead>
<tr>
<th></th>
<th>CCR4+</th>
<th>CXCR3+</th>
<th>Total</th>
<th>Both CCR4+ and CXCR3+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Precursor T-cell neoplasms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precursor T lymphoblastic lymphoma</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>4</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Mature T-cell and NK-cell neoplasms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extranodal NK/T cell lymphoma, nasal type</td>
<td>1 (3.7%)</td>
<td>4 (14.8%)</td>
<td>27</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>MF in transformation</td>
<td>7 (41.2%)</td>
<td>1 (5.9%)</td>
<td>17</td>
<td>1 (5.9%)</td>
</tr>
<tr>
<td>ALCL, ALK+</td>
<td>1 (4.2%)</td>
<td>0 (0%)</td>
<td>24</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>ALCL, ALK−</td>
<td>8 (66.7%)</td>
<td>1 (8.3%)</td>
<td>12</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>PTCCLU</td>
<td>19 (38.0%)</td>
<td>18 (36.0%)</td>
<td>50</td>
<td>6 (12.0%)</td>
</tr>
<tr>
<td>AILT</td>
<td>8 (34.8%)</td>
<td>17 (73.9%)</td>
<td>23</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td><strong>Other types of T- and NK-cell lymphomas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cases</td>
<td>49 (29.0%)</td>
<td>44 (26.0%)</td>
<td>169</td>
<td>17 (10.1%)</td>
</tr>
<tr>
<td>ATLL†</td>
<td>1 (88.3%)</td>
<td>5 (4.9%)</td>
<td>103</td>
<td>4 (3.9%)</td>
</tr>
</tbody>
</table>

* Other types of T and NK-cell lymphoma consist of 1 case with aggressive NK cell leukemia, two cases with enteropathy-type T-cell lymphoma, one case with hepatosplenic T-cell lymphoma, one case of subcutaneous panniculitis-like T-cell lymphoma, and seven cases with primary cutaneous ALCL.

† Data from Ishida et al. (18).
Statistical Analysis. The significance of differences between chemokine-receptor expression-positive and -negative groups was examined using the Fisher exact test or the Mann-Whitney U test. The survival data of patients were analyzed according to the Kaplan-Meier method and were compared using the log-rank and Breslow-Gehan-Wilcoxon tests. Univariate and multivariate analyses were performed with the Cox proportional hazard regression model, and independence of the variables was determined in the latter multivariate analysis using the stepwise method. The correlations between copy-number ratios of CCR4 and FoxP3, CXCR3 and FoxP3, and CCR4 and CXCR3 were examined using the Spearman rank correlation coefficient. Data were analyzed with the aid of StatView software (version 5.0, SAS Institute, Cary, NC). In this study, $P < 0.05$ was considered significant.

RESULTS

CXCR3 and CCR4 Expression in T-Cell and NK-Cell Lymphomas. In this study we analyzed expression patterns of the Th1-associated CXCR3 and Th2-associated CCR4 chemokine receptors in 169 cases of T- and NK-cell lymphoma other than ATLL. As shown in Table 1, both chemokine receptors were rarely expressed in the precursor T-cell lymphoblastic leukaemia/lymphoma, extranodal NK/T-cell lymphoma, nasal type, and ALK$^+$-ALCL. These three lymphoma subtypes are the best defined by clinical, histological, immunological, and genetic features of the T- and NK-cell lymphoma category. Angioimmunoblastic T-cell lymphoma (AILT) cases showed a CXCR3-dominant expression pattern, whereas ALK$^+$-ALCL and MF in transformation exhibited a CCR4-dominant expression pattern. In 50 cases of PTCLU, CXCR3 and CCR4 were detected with similar positivities, 18 cases (36%) and 19 cases (38%), respectively. Figure 1 shows representative expression patterns of CXCR3 and CCR4 in AILT, ALK$^+$-ALCL, MF-in transformation, and PTCLU. For other subtypes of T-cell and NK-cell lymphoma including aggressive NK-cell leukemia, enteropathy-type T-cell lymphoma, hepatosplenic T-cell lymphoma, s.c. panniculitis-like T-cell lymphoma, and primary cutaneous anaplastic large cell lymphoma (ALCL), CXCR3 and CCR4 were expressed in zero of one and zero of one, two of two and two of two, zero of one and zero of one, zero of one and one of one, and one of seven and two of seven cases, respectively.

Clinical Features of 50 PTCLU Patients. Among the 50 PTCLU patients, there were 23 males and 27 females with a median age at diagnosis of 62 years (range, 16–91 years). The clinical characteristics of the patients are summarized in Table 2. The overall survival (OS) curve for all PTCLU patients enrolled in this study is shown in Fig. 2A. The 50% survival ± SE was 7.7 ± 1.3 months.

Comparison of Clinical Characteristics According to CXCR3 and CCR4 Expression in PTCLU. Negative CXCR3 expression was associated with the presence of anemia (Hb < 12 g/dl; $P = 0.0122$), whereas other clinical characteristics did not show significant differences between CXCR3-positive and -negative cases. On the other hand, none of the clinical characteristics investigated in this study showed significant differences between CCR4 -positive and -negative cases. Regarding involved organs, the CXCR3-negative cases showed frequent splenic involvement ($P = 0.0180$). On the other hand, CCR4 status showed no significant association with any particular organs studied. CD25 was expressed in 9 of 13 (69.2%) CCR4 -positive cases and 6 of 31 (19.4%) CCR4 -negative cases, giving a significant association between the two ($P = 0.0038$), whereas no significant association was shown between CXCR3 and CD25 expression.

The OS according to CXCR3 status is shown in Fig. 2B. The 50% OS for CXCR3-positive cases was 24.4 ± 14.3 months, and for CXCR3-negative cases it was 6.7 ± 0.6 months. The OS according to CCR4 status is shown in Fig. 2C. The OS was significantly shorter in the CCR4-positive cases than in the CCR4-negative cases (50% OS; 4.2 ± 0.6 months versus 14.2 ± 3.7 months). Six of 50 (12.0%) cases were positive for both CXCR3 and CCR4. These double-positive cases behaved like the CCR4 -positive subset (50% OS; 4.2 ± 1.0 months). CD25 status did not have a prognostic impact. We further analyzed the OS according to CCR4 and international prognostic index (IPI) status. Among patients with high IPI scores from 3 to 5, the CCR4-positive cases also showed a significantly poorer prognosis than did the CCR4-negative cases (50% OS; 3.0 ± 1.1 months versus 6.7 ± 0.4 months), as shown in Fig. 2D.
Prognostic Factors for PTCLU. Univariate Cox proportional hazard analysis identified the following unfavorable prognostic factors with respect to the survival of patients: presence of B symptoms, LDH level $>\text{upper limit of normal}$, presence of anemia (Hb value $<12 \text{ g/dl}$), presence of leukocytopenia (WBC count $<3.0 \times 10^3/\mu l$), presence of thrombocytopenia (Plt count $<150 \times 10^3/\mu l$), positivity for CCR4 expression, negativity for CXCR3 expression, and high IPI score from 3 to 5 (Table 3). Multivariate analysis showed the presence of B symptoms, LDH level $>\text{upper limit of normal}$, presence of anemia, and positive CCR4 expression to be independent, and significant factors suggesting a poor prognosis (Table 3). Negative CXCR3 expression was not selected as an independent factor in the multivariate analysis. Multivariate Cox proportional hazard analysis including positive CCR4 expression, and high IPI showed that these two unfavorable factors are independent (positive CCR4 expression: HR $= 2.749$; 95% confidence interval $2.034–9.196$; $P = 0.0001$).

Correlation between CCR4 and FoxP3 mRNA Expression in PTCLU. Using quantitative RT-PCR, we analyzed CCR4, CXCR3, and FoxP3 mRNA levels in the affected lymph node cells obtained from 10 patients with PTCLU. According to the Spearman rank correlation coefficient, there was a significant correlation between CCR4 and FoxP3 mRNA expression (Fig. 3A). There was no significant correlation between CXCR3 and FoxP3 mRNA expression (Fig. 3B) or between CXCR3 and CCR4 mRNA expression (Fig. 3C).

DISCUSSION

Considering that CXCR3 and CCR4 are chemokine receptors expressed in functional subsets of CD4$^+$ T cells, it is conceivable that neither of the chemokine receptors would be expressed in T-cell lymphoblastic leukaemia/lymphoma or ex-
transnodal NK/T cell lymphoma, because the former is derived from the earliest stage of T-cell differentiation (28) and the latter from activated NK cells with the germline configuration of T-cell receptor genes (29). ALK⁺-ALCL also showed a double-negative expression pattern. ALK⁺-ALCL is considered to constitute a homogeneous group characterized by overexpression of anaplastic lymphoma kinase (ALK), a tyrosine kinase receptor belonging to the insulin receptor subfamily (30). However, the cell origin has not been well elucidated, and the tumor has unique features that are different from most of the other T-cell lymphoma subtypes, including loss of several pan T-cell markers, positive expression of international prognostic index, cytotoxic molecule expression, and a particularly good prognosis for the patients (31). ALK⁻-ALCL and MF in transformation exhibited a CCR4-dominant expression. ALK⁻-ALCL showed a considerably different chemokine receptor expression pattern from ALK⁺-ALCL, suggesting that ALK⁻-ALCL may form a different clinicopathological group from ALK⁺-ALCL, although both ALK⁺ and ALK⁻-ALCLs are included in the same category of ALCL in the present WHO classification (31). MF is the most common T-cell lymphoma that arises primarily in the skin, and presents with distinctive features including a long natural history, the presence of CD4⁺ and CD8⁺ cells, and negative expression of cytotoxic molecules (32). These features are similar to those of ATL, which show distinctive CCR4-dominant pattern (18, 19). Among all subtypes studied, only AILT showed a CXCR3-dominant expression pattern. This positive CXCR3 expression pattern has also been described recently elsewhere (16, 17). Because the histological diagnosis of AILT may be difficult, especially in the early phase of the disease, CXCR3 is expected to become a useful, objective criterion for the diagnosis of AILT.

With no reproducible criteria for classification, various morphological subtypes of T-cell lymphomas are united into the PTCLU designation, which remains a heterogeneous group within the WHO classification scheme. This heterogeneity seems to be reflected in the chemokine receptor expression patterns for CXCR3 and CCR4. The most important finding in this study is that CCR4 expression, as detected by immunohistochemistry on paraffin sections, was found to be an unfavorable prognostic factor for PTCLU patients. The multivariate survival analysis clarified its independence from the IPI as an unfavorable prognostic factor. An association of CCR4 expression with a poor prognosis was also shown in our ATLL study (18). PTCLU cases showing CXCR3 expression were shown to pursue a more favorable clinical course, although CXCR3 was not selected as an independent factor in the multivariate analysis. The CXCR3 expression frequency seen in AILT cases may explain why some AILT patients have a relatively favorable outcome compared with patients with other types of T-cell lymphoma (33). These data suggest that CXCR3 and CCR4 expression is associated not only with lymphoma subtypes but also with clinical aggressiveness of the tumor. CCR4 seems to be more important than CXCR3 in predicting the prognosis for PTCLU patients.

In this study, we provide preliminary data suggesting a possible association between CCR4 and FoxP3 mRNA expression in PTCLU. FoxP3 appears to be a master gene directing developmental pathways of CD4⁺CD25⁺ Treg cells. We also showed that CCR4 expression was significantly associated with CD25 expression in PTCLU. Retroviral gene transfer of FoxP3 converts naïve T cells toward natural Treg-like cells that suppress the proliferation of other T cells in vitro, and the development of autoimmune disease and inflammatory bowel disease in vivo (34). Thus, it can be envisaged that FoxP3-expressing tumor cells would form a profound immunosuppressive environment around tumor cells so that they can escape from the immunosurveillance of the host. Suppression of the host’s normal effector T cells by FoxP3-expressing tumor cells can result in a severe immunocompromised state, thereby leading to a poor prognosis for these patients.

To apply CCR4 to molecular target therapy, we recently established a mouse-human chimeric anti-CCR4 MoAb (25). This chimeric MoAb has a Fc region that is artificially defucosylated to enhance antibody-dependent cellular cytotoxicity activity by increasing its binding affinity to FcγR on effector cells (25, 35). It showed a robust enhance antibody-dependent cellular cytotoxicity activity against CCR4-positive T-cell leukemia/lymphoma lines obtained using human peripheral blood mononuclear cells as effector cells for both in vitro and in vivo mouse models (25). A novel specific therapy using this chimeric MoAb to target T-cell lymphoma expressing CCR4 molecule is currently being prepared for clinical trials. In the present study,
we show that CCR4 expression is frequently seen in MF in transformation, ALK⁺/⁻ALCL, and PTCLu as well as in ATLL, and these lymphoma subtypes comprise targets for our novel molecular target therapy. CCR4 immunohistochemistry that is applicable to paraffin sections will be of great help in selecting patients suitable for this therapy.

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