Altered Expression of Class I HLA Antigen on Peripheral Mononuclear Cells in Patients with Adult T-Cell Leukemia: Inverse Relationship with Natural Killer Susceptibility

Hisamitsu Uno,1 Hitoshi Matsuoka, Muneou Suzuki, Kazunori Tsuda, and Hirohito Tsubouchi
Second Department of Internal Medicine, Miyazaki Medical School, 5200 Kihara, Kiyotake-cho, Miyazaki, 889-16 Japan

Abstract
Patients with adult T-cell leukemia showed altered expression of class I HLA antigen in their peripheral blood lymphocytes. Acute type adult T-cell leukemia showed increased levels of the antigen expression compared to those of control group and smoldering type (P < 0.001 and 0.01, respectively). Natural killer sensitivity of infected cell lines with different levels of class I HLA expression showed an inverse relationship with the antigen expression. Further, various cell lines including human T-cell leukemia virus type I-infected cell lines treated with acid buffer, which selectively eliminated the surface class I HLA molecules from cell membrane, became more sensitive to natural killer-mediated lysis. These data suggested that the enhanced expression of class I HLA on peripheral blood lymphocytes of patients with acute type adult T-cell leukemia may contribute to escaping from the immunosurveillance system of natural killer cells in vivo.

Introduction
ATL2 is one of the very few virus-associated human cancers that have been found consistently to harbor viruses. ATL is a malignancy of T-cell origin affecting adults in whom HTLV-I retrovirus was identified as an etiological agent (1, 2). It has been reported that several cell activation antigens varied according to the clinical stages of ATL, and the levels of some antigens correlated with specific clinical types. Further, the altered expression HLA-DR antigen at ATL cells was reported (3). However, there has been no report on the change of class I HLA antigen expression at various clinical stages of ATL. Previously, we demonstrated the altered expression of class I HLA antigens on peripheral lymphocytes of patients with ATL where either additional antigens or decreased expression was noted by microcytotoxicity method (4).

Previously, we demonstrated that NK activity of PMNCs from patients with ATL (HTLV-I carriers) was reduced against the NK-sensitive non-HTLV-I-producing target cells compared with that of healthy controls. All three groups, however, did not exhibit significant NK-mediated lysis against HTLV-I-producing cells, indicating that HTLV-I-producing cells with well expressed class I antigen are resistant to NK-mediated lysis (5). Several clinical as well experimental studies suggested an inverse relationship between expression of class I MHC antigen and NK sensitivity (6–11).

Here we report that the expression of class I HLA antigen on PMNCs from patients with ATL varies according to the clinical types of ATL. We demonstrated that the susceptibility of HTLV-I-infected cells to NK-mediated lysis was inversely proportional to their surface expression of class I HLA antigen. Further, the effect of class I HLA expression of HTLV-I-infected cells on NK-mediated lysis did not reside in the ability to form NK-effector conjugates but in an effect of increased postbinding target cell lysis.

Subjects and Methods
Human Subjects and Patients. Thirty-two patients with ATL were subtyped clinically based on accepted criteria for clinical, hematological, and laboratory findings (12). Ten patients with acute ATL (including 7 patients with lymphoma type), 10 patients with chronic ATL, and 12 patients with smoldering ATL were investigated for expression of class I HLA on their PMNCs. Seven anti-HTLV-I-seropositive persons were also studied as healthy carriers. Five anti-HTLV-I-seronegative healthy individuals were used as control group.

Cell Lines. MT-1, MT-2, HUT-102 (B2 clone), and FN were HTLV-I-producing T-CLs. MT-1 and MT-2 were established from cord-blood lymphocytes by cocultivation with T cells from a patient with ATL (13, 14). HUT-102 was established directly from a patient with cutaneous T-cell lymphoma (15). FN was established in our laboratory from peripheral blood of a patient with acute type ATL (4). K562 and Molt-4 are NK-sensitive target CLs derived from a patient with chronic myelocytic leukemia (16) and a patient with acute lymphocytic leukemia (17), respectively. Jurkat is a human T-cell leukemia line derived from a patient with acute lymphoblastic leukemia (18). Sh and Wa are EBV-transformed B-CLs derived from healthy individuals. Daudi is also a B lymphoblastoid CL derived from a patient with Burkitt lymphoma. This CL does not express class I HLA antigen because of deficient β2 microglobulin production, but it does express class II HLA antigens (19).

Cell Preparation. PMNCs were separated from heparinized blood by standard technique with the use of Ficoll-Conray. PMNCs were suspended in RPMI 1640 with 10% FCS supplemented with penicillin, streptomycin, and L-glutamine. Adherent cells were removed by panning PMNCs in a plastic dish for 1 h at 37°C in 5% CO2. Then nonadherent cells obtained were
The addition of 1 % BSA to the buffer was critical to prevent the chain and /37 microglobulin: anti-HLA-DR [(IgG2a, Becton mAbs. mAbs against HLA antigens were: anti-class I HLA or were incubated further with FITC-conjugated F(ab'), goat anti-deterioration of cell viability (20). M(A32.2.b) were obtained from Dr S. M. Fu (University of Virginia, Charlottesville, VA).

Buffered Solution at pH 3.0 and Cell Treatment. An acid solution with a pH 3.0 was made with 0.2 m citric acid-NaH2PO4 buffer containing 1% (w/v) BSA. Cell pellets containing 1–10 X 10^6 cells were added to 0.5 ml of the buffered solution at 4°C for 2 min. The exposed cells were neutralized immediately with the excess medium and washed three times. The addition of 1% BSA to the buffer was critical to prevent the deterioration of cell viability (20).

Immunofluorescence Analysis. Cells were stained with mAbs at 4°C for 30 min. After extensive washing, the cells were incubated further with FITC-conjugated F(ab')2 goat anti-mouse immunoglobulin antibodies at 4°C for 30 min. After extensive washing, the cells were analyzed with a FACScan (Becton Dickinson Immunocytometry Systems) or a FACS Analyzer (Becton Dickinson Immunocytometry Systems).

Immunoprecipitation. Cells were labeled with 125I (DuPont New England Nuclear, Boston, MA) by the lactoperoxidase technique (21). The labeled cells were washed with PBS containing 1 mm phenylmethylsulfonyl fluoride, 10 mM iodoacetamide, and 0.02% Na2S2O4. The cell lysates were prepared by detergent lysis in a lysis buffer containing 20 mM Tris-HCl (pH 7.5), 0.15 M NaCl, 7.5 mM 3-(3-cholamidopropyl)dimethylammonium-1-propansulfonate dihydrate, 50 mM iodoacetamide, 1 mM phenylmethylsulfonyl fluoride, 1 unit/ml aprotinin, 10 μg/ml leupeptin, 50 μg/ml trypsin inhibitor, and 2 mM EDTA. After centrifugation, the lysates were precleared three times with Sepharose-4B conjugated with goat anti-mouse immunoglobulin antibodies. The precleared lysates were added to Sepharose 4B conjugated with goat anti-mouse immunoglobulin antibodies that had been incubated with anti-HLA mAb. The mixture was incubated for 60 min at 4°C and then washed 6 times with a buffer containing 10 mM Tris-HCl (pH 7.8) and 0.6 M NaCl. Three additional washings with a buffer containing 10 mM Tris-HCl (pH 8.8), 0.6 M NaCl, 0.1% SDS, and 0.05% NP40 were carried out. The absorbed proteins were released by boiling for 5 min in sample buffer containing 0.125 mM Tris-HCl (pH 6.8), 2% SDS, and 10% glycerol. SDS-PAGE was carried out on 12.5% polyacrylamide gel with the use of the Bio-Rad Mini Protean I system (Bio-Rad Laboratories, Richmond, CA). The proteins were transferred to nitrocellulose membranes by the electroblotting method (22). The blots were exposed to X-ray film (Eastman Kodak, Rochester, NY). The corrected mean MFI of each group was determined by substitution of 100 cpm of Triton X-100 (Sigma Chemical Co., St. Louis, MO). Each cpm was the mean value of triplicate.

Target-binding Assay. PMNCs depleted of adherent cells were fractionated further on Percoll (Pharmacia, Uppsala, Sweden) density gradients; percentages of osmolality-adjusted Percoll in the medium were 50, 47.5, 45, 42.5, 40, and 37.5% (22). The gradients were spun down at 1,600 rpm for 45 min. The bottom 37.5% layer, which was enriched in LGLS as determined by substitution of 100 μl of Triton X-100 (Sigma Chemical Co., St. Louis, MO) and counted for 1 min in a γ counter. The cytotoxic activity was calculated as follows:

\[
\text{% Cytolysis} = \frac{\text{test cpm} - \text{spontaneous cpm}}{\text{total cpm} - \text{spontaneous cpm}} \times 100
\]

where the spontaneous cpm was measured by the incubation without addition of effector cells, and the total cpm was determined by substitution of 100 μl of Triton X-100 (Sigma Chemical Co., St. Louis, MO). Each cpm was the mean value of triplicate.

Statistical Analysis. Comparisons between unpaired sample groups was by the Wilcoxon rank sum (two-tailed) test where appropriate. Correlation was tested using the Spearman rank correlation coefficient.

Results

Class I HLA Expression on PMNCs from Patients with ATL. The expression of class I HLA antigen on PMNCs from patients with ATL was studied by immunofluorescence analysis. MFI varied among subtypes of ATL (Fig. 1). Patients with acute type showed significantly high MFI compared to those of smoldering type and healthy individuals (P < 0.01 and 0.001, respectively). The MFI of patients with smoldering and chronic types varied from high to low intensities. The mean ± SD of abnormal lymphocyte percentage in the peripheral blood of smoldering, chronic, acute types, and HTLV-I-positive healthy carriers was 7.55 ± 6.70, 30.32 ± 29.32, 25.28 ± 29.49, and 10.99 ± 4.99, respectively. Bars, mean MFI of each group. * P < 0.01; ** P < 0.001.
0.67 ± 0.82, respectively. The correlation coefficient of each subtype between abnormal lymphocytes and MFI was −0.33 for smoldering type, −0.01 for chronic type, −0.52 for acute type, and 0.19 for carriers. Thus, there was no correlation between the expression of class I HLA and the proportion of leukemic cells in the peripheral blood.

**Relationships between Expression of Class I HLA Antigen and NK Susceptibility in HTLV-I-infected Cells.** Two HTLV-I-infected CLs, MT-2 and FN, were studied for their susceptibility to NK-mediated lysis. Although MT-2 showed almost no NK susceptibility, FN showed low level of susceptibility to NK cells (Fig. 2A). This figure was representative of three separate experiments using three different effectors in which FN was always more sensitive to effectors than was MT-2. Flow cytometric analysis of cell surface HLA antigens with anti-class I, anti-DR, and anti-DQ mAbs revealed that the expression of class I HLA antigen of FN is apparently lower than that of MT-2, whereas the MFI of class II HLA antigens did not differ from each other (Fig. 2B).

**Selective Elimination of Class I HLA Antigen from Cell Membrane by Acid Buffer Treatment.** When fresh PMNCs or CLs were treated with citric acid, the antigenicity of class I HLA molecules but not that of class II HLA and other non-HLA antigens was eliminated specifically from cell surface membrane (Table 1). Fresh PMNCs, MT-I, Jurkat, and Molt-4 expressed high percentage of class I HLA antigen-positive cells. After the treatment with the acid buffer, the percentage of class I HLA antigen-positive cells in these cells was decreased remarkably, whereas the percentages of HLA-DR-, CD2-, and CD3-positive cells remained unchanged irrespective of the treatment. Daudi expressed only HLA-DR antigen, the expression of which showed no change by the treatment. K562, which is very susceptible to NK-mediated lysis, did not express class I HLA, HLA-DR, CD2, or CD3 antigens. In an experiment (data not shown), β2 microglobulin on MT-2 showed the same change with class I HLA antigen.

**Cell Viability and Regeneration of Class I HLA Antigens after Acid Buffer Treatment.** The effect of acid buffer treatment on cell viability was examined to exclude the possibility that the treatment may influence the NK assay system. The viability of cells did not change at least for 4 h when incubated in the medium after the treatment at either 37°C in a humidified 5% CO₂ atmosphere or 4°C in room air.

Furthermore, the time course of the regeneration of surface class I HLA antigen after acid treatment was studied with the

### Table 1  Altered expression of HLA class I antigens on fresh PMNC and cell lines with acid treatment

<table>
<thead>
<tr>
<th>Cells</th>
<th>Surface antigens</th>
<th>Fluorescence-positive cells (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before pH 3.0</td>
<td>After pH 3.0</td>
</tr>
<tr>
<td>Fresh PMNC</td>
<td>Class I HLA</td>
<td>91.9</td>
</tr>
<tr>
<td></td>
<td>HLA-DR</td>
<td>12.6</td>
</tr>
<tr>
<td></td>
<td>CD2</td>
<td>70.8</td>
</tr>
<tr>
<td></td>
<td>CD3</td>
<td>59.9</td>
</tr>
<tr>
<td>MT-1</td>
<td>Class I HLA</td>
<td>87.5</td>
</tr>
<tr>
<td></td>
<td>HLA-DR</td>
<td>83.7</td>
</tr>
<tr>
<td></td>
<td>CD2</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>CD3</td>
<td>5.0</td>
</tr>
<tr>
<td>Jurkat</td>
<td>Class I HLA</td>
<td>98.1</td>
</tr>
<tr>
<td></td>
<td>HLA-DR</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>CD2</td>
<td>97.9</td>
</tr>
<tr>
<td></td>
<td>CD3</td>
<td>68.8</td>
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<tr>
<td>Molt-4</td>
<td>Class I HLA</td>
<td>93.8</td>
</tr>
<tr>
<td></td>
<td>HLA-DR</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>CD2</td>
<td>13.6</td>
</tr>
<tr>
<td></td>
<td>CD3</td>
<td>87.4</td>
</tr>
<tr>
<td>K562</td>
<td>Class I HLA</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>HLA-DR</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>CD2</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>CD3</td>
<td>0.4</td>
</tr>
<tr>
<td>Daudi</td>
<td>Class I HLA</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>HLA-DR</td>
<td>95.7</td>
</tr>
<tr>
<td></td>
<td>CD2</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>CD3</td>
<td>1.0</td>
</tr>
</tbody>
</table>

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Fig. 2. NK susceptibility and class I HLA antigen expression in HTLV-I-infected T-cell lines. A, in vitro killing of MT-2 and FN with nonadherent PMNC effector cells from a HTLV-I-negative healthy person. Points, means of triplicates. B, flow cytometric analysis of MT-2 and FN CLs labeled with anti-class I HLA, anti-DR, and anti-DQ mAbs.
use of Molt-4 and Jurkat, which expressed a high density of class I HLA antigen. The acid-exposed cells were incubated in the medium at either 37°C in an incubator or 4°C in room air. The regeneration of class I HLA antigen was determined by relative proportions of the antigen-positive cells before and after the treatment with the use of a flow cytometer. After 4-h incubation at 37°C, which is the condition of NK-mediated lysis, about 60% of the maximal expression of class I HLA antigen regenerated on the membrane surface of cells. After 4-h incubation at 37°C, class I HLA antigen recovered gradually, and the recovery rate was more than 80% after 24-h incubation. On the other hand, the incubation at 4°C did not induce significant restoration until 12 h. After 24-h incubation at 4°C, about 40% of cells showed recovery of class I HLA antigen. Consequently, target cells used for the NK assay were incubated at 4°C until they were subjected to the NK assay.

**Immunoprecipitation of Class I HLA Antigen on the Membrane Surface of Cells Treated with Acid Buffer.** In order to ascertain the reduction of class I HLA antigen on the membrane surface of cells by acid treatment, Molt-4 cells were labeled with 125I by the lactoperoxidase method, treated with or without acid buffer, and washed three times. The detergent lysates were immunoprecipitated with anti-class I HLA mAb and then analyzed by SDS-PAGE. Anti-class I HLA mAb precipitated M, 45,000 and 11,500 polypeptides in untreated Molt-4, which are the heavy chain and β2 microglobulin of class I HLA molecules, respectively (Fig. 3, Lane b). On the other hand, Molt-4 cells treated with acid buffer did not express enough membrane surface class I HLA antigen to be detected by immunoprecipitation (Fig. 3, Lane a).

**Class I HLA Antigen Expression and Susceptibility to NK-mediated Lysis in Various CLs.** CLs that differed in their relative levels of class I HLA antigen expression were examined for their susceptibility to NK-mediated lysis. An inverse correlation between NK susceptibility and the levels of class I HLA antigen expression on target cells was observed (Fig. 4, □). It should be noted that the acid treatment of target CLs had no effect on the spontaneous release from the cells.

**Increased NK Susceptibility of Class I HLA-eliminated CLs.** To confirm the role of class I HLA antigen in NK-mediated lysis, CLs with reduced class I HLA antigen expression by acid treatment were also subjected to NK-mediated lysis as target cells (Fig. 4, □). When Molt-4, FN, Wa, MT-2, and HUT-102 were treated with acid buffer, these CLs lost their surface class I HLA antigen and became more sensitive to NK cell killing in proportion to the degree of decreased expression of the antigen. On the other hand, K562, which expressed trace amounts of class I HLA antigen, did not significantly increase the already enhanced NK cell sensitivity after such treatment.

**Target-binding Assay.** To define the level at which class I HLA antigen is involved in the process of NK-mediated lysis, we examined whether the expression of class I HLA antigen on target cells influences the efficiency of the formation of NK-target cell conjugates. Purified LGLs were used as effectors for target-binding assay. As shown in Table 2, K562 and MT-2, which had different levels of class I HLA antigen expression, showed almost no change in the percentage of LGL-target cell conjugates regardless of acid treatment, indicating that the expression of the antigen did not influence the formation of NK-target conjugates.

**Discussion**

Thus far, the change of class I HLA antigen on ATL cells and its biological significance have not been verified. In the present study, we examined the expression of class I antigen of PMNCs by immunofluorescence in patients with various types of ATL. The patients showed variety in their expression of the antigen. In particular, patients of acute type revealed significantly increased expression of the antigen. Unfortunately, we could not type the class I HLA antigens in the present patient group. However, we reported previously that the frequency of HLA-Bw62 was increased significantly in acute ATL (4). Therefore, it is possible that this HLA antigen might be increased in acute ATL patients with increased expression of class I HLA antigen. It is also important to note that the increased expression of class I HLA antigen appears to be related to the disease progression rather than to HTLV-I infection since the virus carriers showed no significant increase of the antigen compared to healthy controls.

Although the quantity of HLA class I antigens in various types of leukemic cells has been investigated, no correlation was found between the quantitative expression of class I antigen and the stage of maturation in each cell type; nor was any correlation found between the quantitative expression of class I antigens on the leukemic cells and the proliferation of leukemic cells in the peripheral blood (23, 24). The present study, there-
of the antigen. The time course of the regeneration of surface class I HLA expression in proportion to the degree of decreased expression showed different expression of HLA-DR and HLA-DQ antigens, which indicated that in HTLV-I-infected T cells an inverse relationship existed between expression of class I HLA antigen and NK susceptibility (P < 0.0001). The correlation coefficient between the expression of HLA antigens and NK susceptibility was -0.88 (P < 0.0001), where K562 and MOLT-4 were excluded from the calculation because of their already high degree of expression.

Table 2 Effect of class I HLA antigen expression on LGL-target binding

<table>
<thead>
<tr>
<th>Target</th>
<th>Donor 1</th>
<th>Donor 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>K562</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>62.0</td>
<td>65.0</td>
</tr>
<tr>
<td>Acid buffer</td>
<td>66.3</td>
<td>66.6</td>
</tr>
<tr>
<td>MT-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>88.6</td>
<td>71.4</td>
</tr>
<tr>
<td>Acid buffer</td>
<td>75.5</td>
<td>73.2</td>
</tr>
</tbody>
</table>

* LGL from PBLs depleted of adherent cells were purified on Percoll gradients and used as effectors for target-binding assay. The percentage of conjugated LGL (LGL conjugates/target cells) was estimated by using a hemocytometer.

Therefore, the first report on the association between the quantitative expression of class I HLA antigen and a human T-cell hematopoietic malignancy.

We examined NK activity against HTLV-I-producing cells with regard to the degree of HLA expression on the cells. Two HTLV-I-infected CLs, MT-2 and FN, which differed in their expression of class I HLA antigen but not in the expression of HLA-DR and HLA-DQ antigens, showed different sensitivity to NK-mediated lysis in inverse proportion to their expression of class I HLA antigen. Further, another 5 CLs with different levels of class I HLA antigen showed inverse relationships between expression of the antigen and NK susceptibility. Our results indicated that in HTLV-I-infected T cells an inverse relationship existed between expression of class I HLA antigen and susceptibility to NK-mediated lysis.

Since it is difficult to establish interleukin 2-independent, HTLV-I-infected T CLs that specifically differ in their levels of class I HLA expression, we used a simple, reproducible method by which the antigenicity of class I HLA molecules was eliminated selectively from the membrane surface of viable cells treated with acid buffer. It was not probable that the treatment would influence the NK assay system because the viability of cells did not change at least for 4 h when incubated in the medium after the treatment. When CLs that express class I HLA antigen were treated with acid buffer, those CLs lost their surface class I HLA antigen and became more sensitive to NK cell killing in proportion to the degree of decreased expression of the antigen. The time course of the regeneration of surface class I HLA antigen in the acid-exposed cells showed that the antigen expression of target cells was recovered partially during the incubation period of the NK-mediated lysis system, indicating that the early expression of class I HLA antigen at target cells played a critical role in the interaction between target cells and NK cells to bring out an enhancing NK effect.

Different types of experiments have been carried out to investigate the relationship between susceptibility to NK-mediated lysis and target cell class I HLA expression, in which various procedures were used to produce alterations of MHC products of target cells. However, treatments such as chemical agents, cytokines, and viruses have pleiotropic effects, i.e., a variety of phenotypic changes, in addition to increased class I MHC expression. We also could not exclude the possibility of the pleiotropic effect in the acid treatment. It is interesting to note that the level of target cell class I HLA expression is not sufficient to determine susceptibility or resistance to NK-mediated lysis of some kinds of target cells.

To examine the mechanism that enable NK cells to become more cytotoxic against class I MHC antigen-eliminated target cells, target-binding assay was carried out and found that class I MHC antigen-eliminated target cells did not acquire high binding affinity to NK cells. Our results are compatible with the data obtained by other investigators (8–10). However, opposite results have been described, where the interference of class I HLA antigen in the natural cytotoxic process might occur in the binding step of the cytotoxic process (11). It is possible that these conflicting observations could have arisen if the maneuvers used to alter class I antigen expression in the different tumor cell lines variably altered expression of other membrane molecules involved in NK-mediated lysis.

In vivo, the activity of at least two types of immunological effector cells appears to be dependent on the expression of MHC class I antigens by the target cells. The biological significance of altered expression of class I MHC in vivo has been reported in murine hematopoietic malignancies (26–28) and some human hematopoietic malignancy (29), as concerned T-cell cytotoxic and NK activities. CTLs require expression of MHC class I to kill target cells, whereas high levels of MHC class I antigens may inhibit NK cells from killing tumor cells in vivo. The present study indicated that surface class I MHC antigen on HTLV-I-infected cells demonstrated important immunoregulatory molecules in vivo not only for CTL but also for NK cells in ATL. HLA-restricted associative recognition of target antigens expressed on the leukemic cells was demon-
strated by the fact that the cytotoxic activity by CTLs required target tumor cells not only infected with HTLV-I but also sharing HLA antigens in common with CTLs (30–32). ATL cells with decreased expression of class I MHC gene products are not recognized efficiently and are lysed less by CTL, whereas NK cells may prevent the growth or expansion of these ATL cells that have escaped CTL recognition and lysis. ATL cells with the increased expression of class I HLA in acute type ATL may allow such leukemic cells to escape detection by NK cells. However, ATL cells with increased class I HLA antigen might not be lysed efficiently by CTLs because most T cells in peripheral blood are leukemic cells in patients with acute type ATL.

References

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