Recognition of Minor Histocompatibility Antigens on Lymphocytic and Myeloid Leukemic Cells by Cytotoxic T-Cell Clones

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Clinical studies indicated an enhanced antileukemic effect of allogeneic bone marrow transplantation (BMT), as compared with autologous BMT. After allogeneic HLA-identical BMT, donor-derived cytotoxic T lymphocytes (CTLs) directed at minor histocompatibility (mH) antigens on the recipients, tissues can be shown. To evaluate the antileukemic reactivity of mH antigen-specific CTLs, we analyzed the expression of mH antigens on circulating lymphocytic and myeloid leukemic cells. We show that the defined mH specificities HA-1 through HA-5 and H-Y are present on leukemic cells, indicating that mH antigen-specific CTLs are capable of HLA class I-restricted antigen-specific lysis of leukemic cells. Compared with interleukin-2–stimulated normal lymphocytes, leukemic cells of lymphocytic origin are less susceptible to T-cell–mediated cytotoxicity by the HA-2 mH antigen-specific CTL and the anti–HLA-A2 CTL clone. A possible explanation for this phenomenon is impaired expression of the LFA-1 adhesion molecule. Our study suggests that mH antigen-specific HLA class I–restricted CD8+ CTLs may be involved in the graft-versus-leukemia reactivity after allogeneic BMT.

Bone marrow transplantation (BMT) using allogeneic HLA-identical donors as a treatment modality for hematologic malignancies is complicated by the occurrence of graft-versus-host disease (GVHD). Despite the deleterious effects of GVHD, clinical studies indicate an associated decreased leukemia relapse rate, commonly designated as the graft-versus-leukemia (GVL) effect.4

After allogeneic HLA-identical BMT, donor-derived HLA class I–restricted minor histocompatibility (mH) antigen-specific cytotoxic T lymphocyte (CTL) lines can be generated by stimulating mononuclear cells from the patient post-BMT with irradiated mononuclear cells pre-BMT.5,6 A number of these CTL lines were cloned by limiting dilution.8 CTL clones recognizing the HLA-A2–restricted mH specificities HA-1, HA-2, HA-4, HA-5 (frequencies in a random healthy population: 69%, 95%, 16%, and 7%, respectively), and H-Y, and an HLA-A1–restricted mH antigen-specific CTL clone recognizing HA-3 (frequency: 88%) were characterized. The mH antigens differ in their tissue expression. All mH antigens are expressed on mature blood cells, whereas they are differentially expressed on normal hematopoietic progenitor cells and skin-derived cells.10-12 We have recently shown that mH antigen-specific CTLs may cause BM graft rejection.13 Using these mH antigen-specific CTL clones, we also showed antigen-specific growth inhibition of clonogenic myeloid leukemic cells.14 Recognition of mH antigens on leukemic cells by mH antigen-specific CTLs may explain the GVL effect of allogeneic HLA-identical BMT. To study the recognition of mH antigens on circulating leukemic cells of lymphocytic and myeloid origin, the CTL clones specific for HA-1 to HA-5 and the mH antigen H-Y were used.

We describe here the recognition of these mH antigens on circulating lymphocytic and myeloid leukemic cells by mH antigen-specific CTLs and hypothesize the participation of these CTLs in the GVL effect of allogeneic BMT.

Materials and Methods

Patients and preparation of leukemic samples. Leukemic samples (n = 24) were selected from patients expressing HLA-A1 and/or HLA-A2, which are the HLA class I restriction molecules for mH antigen-specific CTL clones (ie, HLA-A1 for HA-3, and HLA-A2 for HA-1, -2, -4, -5 and H-Y). Six patients with acute myeloid leukemia, 3 patients with chronic myeloid leukemia, 7 patients with acute lymphocytic leukemia, and 8 patients with chronic lymphocytic leukemia (including B-prolymphocytic leukemia and hairy cell leukemia) were tested. Leukemic samples from peripheral blood were obtained after informed consent at diagnosis before therapy. The cells were centrifuged over Ficoll-Isoopaque (density, 1.077 g/mL) and the leukocytes in the interface were subsequently stored in liquid nitrogen. In case of patients with a hairy cell leukemia, spleens were used as a source of leukemic cells. Parts of these spleens were minced, and leukocytes were obtained after Ficoll-Isoopaque density centrifugation and subsequently stored in liquid nitrogen. The number of leukemic cells in all samples was more than 90% as measured by morphology, immunophenotyping, and/or cytogenetic analysis (data not shown).

mH antigen-specific CTL clones. Cytotoxic T-cell lines HA-1 through HA-5 and H-Y were obtained from 5 patients after allogeneic BMT as previously described.35 These T-cell lines were cloned by limiting dilution, as described in detail.3 The CD8+ T-cell receptor α/β+ CTL clones were expanded in culture medium, consisting of RPMI 1640 (Gibco, Grand Island, NJ) supplemented with 15% selected human serum, 20 Cetus units (CU) recombinant interleukin-2 (rIL-2)/mL (EuroCetus, Amsterdam, The Netherlands), 3 mmol/L glutamine, 50 μg/mL gentamycin, and 1 μg/mL leuкоagglutinin A (Pharmacia, Uppsala, Sweden). A fedemix containing irradiated allogeneic peripheral blood mononuclear cells and patient’s irradiated pretransplant Epstein-Barr virus-transformed B-cell line was added. The mH antigen specificity was shown by differential recognition of lymphocytes from various
HLA-identical sibling pairs and population studies. The clones were stored in liquid nitrogen.

To study the recognition of mH antigens on circulating leukemic cells, these mH antigen-specific CTL clones were used. CTL clones with anti-HLA-A1 or anti-HLA-A2 specificity were used as control for the presence of the HLA-class I restriction molecules in the cell-mediated lysis (CML) assays. The day before the CML assay was performed, the clones were thawed and cultured in RPMI 1640 (GIBCO), supplemented with 50 μg/mL gentamycin, 15% selected human serum, and 20 CU rIL-2/mL (Eurocetus).

Preparation of target cells. Thawed leukemic cells were used in all experiments. The leukemic cells were preincubated overnight in RPMI 1640 (GIBCO), supplemented with 10% selected human serum, 3 mmol/L L-glutamine, and 50 μg/mL gentamycin. To obtain normal lymphocytes, leukemic cell suspensions were cultured in culture medium as described above, supplemented with 0.1 μg/mL phytohemagglutinin (Wellcome, Dartford, UK). After 3 days, the cells were washed and expanded in culture medium in the presence of 20 CU rIL-2/mL (Eurocetus) for at least 3 days. The suspensions used contained >90% CD3+ IL-2-stimulated normal lymphocytes (data not shown).

CML. CML assays were performed using a standard 51Cr-release assay. Briefly, target cells were incubated with 100 μCi Na251CrO4 (DuPont NEN Products, Boston, MA) for 1 hour at 37°C and washed. Then, 5 × 103 viable target cells were incubated with CTL clones at different effector to target (E/T) ratios for 4 hours at 37°C. After incubation, the supernatant was collected and radioactivity was measured in a gamma counter. Spontaneous release was measured by incubating target cells in the absence of effector cells, and maximum release was determined by lysing the target cells in a Zaponin solution (Coulter Electronics, Luton, UK). The percentage of specific lysis was calculated as follows: ([experimental release – spontaneous release]/[maximum release – spontaneous release]) × 100%.

In cold target inhibition experiments, nonradioactive (cold) target cells and 51Cr-labeled (hot) target cells at different cold/hot ratios were incubated with effector cells at fixed E/T ratios. In these assays, lymphocytic leukemic cells positive for the HLA class I restriction molecule HLA-A2, but lacking the mH antigen as determined on corresponding IL-2-stimulated normal lymphocytes in a 51Cr-release assay using the mH antigen-specific clones described above, were used as controls for steric hindrance.

To determine the influence of expression of adhesion molecules on CML of IL-2-stimulated normal lymphocytes, blocking studies were performed. Target cells were incubated with radioactive chromium as described above, and 5 × 105 viable target cells per well were subsequently incubated with saturating amounts of monoclonal antibodies against CD11a or CD18 (LFA-1 complex; Central Laboratory for the Blood-transfusion Service CLB, Amsterdam) for 30 minutes at 37°C. As a control, target cells with no antibodies added were run in parallel. Afterwards, the target cells were incubated for 4 hours at 37°C with the HA-2 mH antigen-specific CTL clone at an E/T ratio of 5:1. Thereafter, the supernatant was collected and radioactivity was measured using the procedure previously described.

Immunofluorescence. To estimate the number of HLA-A2 molecules on leukemic cells and IL-2-stimulated normal lymphocytes, viable cells were incubated with saturating amounts of CR11-351 (an anti-HLA-A2/28 monoclonal antibody; courtesy of Dr S. Ferrone, New York Medical College, New York, NY) for 30 minutes at 4°C, washed, subsequently incubated with Goat-antimouse/fluorescein isothiocyanate (FITC) (Becton Dickinson, Mountain View, CA) for 30 minutes at 4°C, and washed. To analyze the expression of adhesion molecules, leukemic cells or IL-2-stimulated normal lymphocytes were incubated with monoclonal antibodies against CD11a and CD18 (LFA-1 complex) and CD54 (ICAM-1; Immunotech, Marseille, France) for 30 minutes at 4°C, washed, incubated with goat-antimouse/FITC for 30 minutes at 4°C, and washed. Control samples were stained with the conjugate only. Finally, the cells were fixed in 1% paraformaldehyde before analysis on a FACScan flow cytometer (Becton Dickinson).

To ensure identical instrument settings and sensitivity for comparison of separate experiments, latex beads with calibrated amounts of FITC molecules (Flow Cytometry Standards Corp, Research Triangle Park, NC) were run before each experiment. Results are given as median fluorescence from the fluorescence histograms.

**Fig 1.** Expression of mH antigens on leukemic cells as compared with corresponding IL-2-stimulated normal lymphocytes. Reactivity of mH antigen-specific CTL clones with lymphocytic leukemias (A) and myeloid leukemias (B), as compared with the corresponding IL-2-stimulated normal lymphocytes (C). Effector to target ratio in the experiments is 5:1. Results are given as the percentage of specific lysis (mean ± SD if more than 4 patients whose IL-2-stimulated normal lymphocytes showed expression of that particular mH antigen; otherwise, when less than 4 patients showed expression of the relevant mH antigen on IL-2-stimulated normal lymphocytes, mean values). All patients were tested at least in duplicate experiments to eliminate variations between the cytotoxicity assays performed on different days.
in arbitrary units on a 4-decade logarithmic scale derived from the fluorescence detectors using the Consort-30 software (Becton Dickinson).

RESULTS

Expression of mH antigens. We compared lysis of leukemic cells and IL-2-stimulated normal lymphocytes derived from the same individual by mH antigen-specific CTL clones and CTL clones recognizing the HLA restriction molecules HLA-A1 and HLA-A2. Results are given in Fig 1A (lymphocytic leukemias) and Fig 1B (myeloid leukemias). All mH antigens present on IL-2-stimulated normal lymphocytes could also be detected on the corresponding leukemia cells. These results also show that mH antigen-specific CTLs can lyse lymphocytic and myeloid leukemia cells. The observation that IL-2-stimulated normal lymphocytes inhibit lysis of radiolabeled IL-2-stimulated normal lymphocytes by the HA-2 mH antigen-specific CTL clone and the anti–HLA-A2 CTL clone in a dose-dependent manner (Fig 2A and B). The decreased sensitivity to lysis by the HA-2 mH antigen-specific CTL clone and the HLA-A2 CTL clone of lymphocytic leukemic cells as compared with that of the corresponding IL-2-stimulated normal lymphocytes is confirmed by these studies. However, cold leukemic cells are less effective in inhibiting lysis of radiolabeled IL-2-stimulated lymphocytes by the CTL clones used. These studies confirm the decreased sensitivity to lysis by the HA-2 mH antigen-specific CTL clone and the anti–HLA-A2 CTL clone of lymphocytic leukemic cells as compared with that of the corresponding IL-2-stimulated normal lymphocytes.

The observation that IL-2-stimulated normal lymphocytes are more susceptible to target cell lysis than the corresponding leukemic cells is further shown in the titration curves in Fig 2C and D.

Immunofluorescence. To explain the decreased susceptibility of lymphocytic leukemic cells to lysis by the HA-2 mH antigen-specific CTL clone and the anti–HLA-A2 CTL clone, we analyzed the expression of the HLA restriction molecule and cellular adhesion molecules. First, the number of HLA-A2 molecules on IL-2-stimulated normal lymphocytes and leukemic cells were compared. The number of HLA-A2 molecules on IL-2-stimulated normal lymphocytes were compared with the number of HLA-A2 molecules on IL-2-stimulated normal lymphocytes.

Table 1. Comparison Between IL-2-Stimulated Normal Lymphocytes and Corresponding Leukemic Cells in Their Susceptibility to Lysis by mH Antigen-Specific CTL Clones and an Anti–HLA-A2 CTL Clone at Different Effector to Target (E/T) Ratios

<table>
<thead>
<tr>
<th>CTL</th>
<th>E/T</th>
<th>NL n = 4</th>
<th>LY n = 4</th>
<th>MY n = 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA-1</td>
<td>5:1</td>
<td>80 ± 19</td>
<td>75 ± 19</td>
<td>58 ± 19</td>
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<tr>
<td></td>
<td>2.5:1</td>
<td>75 ± 19</td>
<td>58 ± 19</td>
<td>45 ± 14</td>
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<td></td>
<td>1:1</td>
<td>60 ± 19</td>
<td>45 ± 19</td>
<td>36 ± 15</td>
</tr>
<tr>
<td>HA-2</td>
<td>5:1</td>
<td>60 ± 19</td>
<td>58 ± 19</td>
<td>46 ± 15</td>
</tr>
<tr>
<td></td>
<td>2.5:1</td>
<td>58 ± 19</td>
<td>48 ± 19</td>
<td>36 ± 15</td>
</tr>
<tr>
<td></td>
<td>1:1</td>
<td>50 ± 19</td>
<td>70 ± 19</td>
<td>70 ± 19</td>
</tr>
<tr>
<td>HA-3</td>
<td>5:1</td>
<td>55 ± 19</td>
<td>49 ± 19</td>
<td>59 ± 19</td>
</tr>
<tr>
<td></td>
<td>2.5:1</td>
<td>53 ± 19</td>
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<td>50 ± 19</td>
<td>49 ± 19</td>
<td>59 ± 19</td>
</tr>
<tr>
<td></td>
<td>2.5:1</td>
<td>48 ± 19</td>
<td>48 ± 19</td>
<td>80 ± 19</td>
</tr>
<tr>
<td></td>
<td>1:1</td>
<td>46 ± 19</td>
<td>70 ± 19</td>
<td>70 ± 19</td>
</tr>
</tbody>
</table>

Values represent the percentage of specific lysis (mean ± SD).

Abbreviations: n, number of patients positive; NS, not significant (paired values at E/T 5:1 and 1.2:1); NT, not tested. NL, normal lymphocytes; LY, lymphocytic; MY, myeloid.
Cold target inhibition experiments: example of 2 patients with lymphocytic leukemias. Cold target experiments were performed to evaluate the sensitivity to CML of lymphocytic leukemic cells. Lysis of radiolabeled IL-2-stimulated normal lymphocytes was inhibited by increasing numbers of (A) "cold" normal lymphocytes, (B) autologous leukemic cells, and (C) third-party leukemic cells. The upper panel represents data from patient KA with a prolymphocytic leukemia; the lower panel from patient MI with an acute lymphocytic leukemia. Effector cells are the HA-2 mH antigen-specific CTL clone ([A] effector to target ratio is 2.5:1; [C] at different ratios) and the anti-HLA-A2 CTL clone recognizing the restriction molecule ([B] effector to target ratio is 2.5:1; [D] at different ratios). Third-party leukemia is cells from a patient with a chronic lymphocytic leukemia, typing HLA-A2 positive but HA-2 negative. (A) Normal lymphocytes; (B) autologous leukemia.

Second, the number of CD11a/CD18 (LFA-1) and CD54 (ICAM-1) adhesion molecules on IL-2–stimulated normal lymphocytes, lymphocytic leukemic cells from 2 patients, and a myeloid leukemic cell was quantified. Results (in arbitrary units) are given in Table 3. The CD11a/CD18 expression of lymphocytic leukemic cells is clearly impaired as compared with those of IL-2–stimulated normal lymphocytes and the myeloid leukemic cell. There are no differences between IL-2–stimulated normal lymphocytes and the leukemic cells in the expression of VLA-1 and CD49B.
(both negative) and CD49D (expressed in uniform quantities on all cells tested).

Blocking studies. To determine the importance of impaired expression of CD11a/CD18 on susceptibility to CML, blocking studies were performed. IL-2-stimulated normal lymphocytes from 2 patients were used as targets for the HA-2 mH antigen-specific CTL clone with and without the addition of monoclonal antibodies against CD11a or CD18. The results are given in Table 4. Blocking of CD11a but in particular of CD18 inhibits lysis by this particular CTL clone, emphasizing the importance of these adhesion molecules.

DISCUSSION

After BMT, donor-derived mH antigen-specific CTL activity directed against the recipient can be shown in particular but not exclusively in patients with chronic GVHD. A number of mH antigens have been characterized. CTL clones specific for the male mH antigen H-Y and the non-sex-linked mH antigens HA-1, HA-2, HA-3, HA-4, and HA-5, which are recognized in a classical HLA class I-restricted fashion, have been generated.28 Using the latter clones, we show in this study that circulating leukemic cells of lymphocytic and myeloid origin express the defined mH antigens that are present on the patient's IL-2-stimulated normal lymphocytes. Therefore, mH antigen-specific CTL clones are capable of exerting potent HLA-restricted antigen-specific lysis of circulating leukemic cells. Recently, we have also shown that mH antigen-specific CTLs can inhibit growth of myeloid clonogenic precursor cells in an antigen-dependent HLA class I-restricted fashion.14 Herewith, our data further support the notion that the antirecipient reactivity after allogeneic BMT includes also leukemic myeloid precursor cells and circulating leukemic cells, and thus may provide an explanation for the GVL effect of allogeneic transplantation.

Compared with IL-2-stimulated normal lymphocytes, leukemic cells of lymphocytic origin are less susceptible to lysis by the HA-2 mH antigen-specific CTL clone, as is shown in Table 1 and Fig 1. However, it should be noted that IL-2-stimulated normal lymphocytes are T lymphocytes, whereas most leukemic lymphocytes are either of B- or T-cell origin. This decreased susceptibility is most pronounced when HA-2 mH antigen-specific lysis of IL-2-stimulated normal lymphocytes and lymphocytic leukemic cells is compared, a phenomenon that did not occur for myeloid leukemic cells.

To analyze this decreased susceptibility to lysis, cold target inhibition experiments were performed. The results from these studies confirm that IL-2-stimulated normal lymphocytes are preferentially lysed by these two clones as compared with IL-2-stimulated normal lymphocytes, because cold lymphocytic leukemic cells in increasing cold/hot ratios hardly inhibit lysis of hot IL-2-stimulated normal lymphocytes (Fig 2). Again, this decreased susceptibility does not exclusively apply for the HA-2 mH antigen-specific CTL clone, because comparable results were obtained with the anti-HLA-A2 CTL clone recognizing the HLA class I restriction molecule (Table 1).
Absence of the HLA restriction molecule leads to escape from lysis by mH antigen-specific CTLs and CTLs recognizing the HLA restriction element.\(^\text{14}\) We therefore enumerated the number of HLA-A2 molecules on the cell surface of IL-2-stimulated normal lymphocytes and lymphocytic leukemic cells from 9 patients. The results show that in all cases the HLA-A2 molecule was present (Table 2) and that there are no differences between IL-2-stimulated normal lymphocytes and lymphocytic leukemic cells in the expression of HLA-A2.

Thus, impaired expression of this restriction molecule appears not to be the mechanism responsible for decreased lysis of lymphocytic leukemic cells as compared with corresponding IL-2-stimulated normal lymphocytes. This is in concordance with the observation that there are no differences in susceptibility to lysis by the HA-1 and HA-3 mH antigen-specific CTL clones between IL-2-stimulated normal lymphocytes and leukemic cells, indicating that impaired expression of the HLA restriction element is unlikely.

We recently showed that hairy cell leukemias lack expression of CD11a, and that induction of CD11a/CD18 (LFA-1) and CD54 (ICAM-1) enhances susceptibility to T-cell-mediated cytolysis.\(^\text{15}\) Therefore, we quantified the number of CD11a/CD18 and CD54 adhesion molecules on IL-2-stimulated normal lymphocytes, lymphocytic leukemic cells, and a myeloid leukemic cell. The expression of CD11a/CD18 is impaired on the lymphocytic leukemic cells of both patients tested as compared with IL-2-stimulated normal lymphocytes. This may contribute to the decreased susceptibility of lymphocytic leukemic cells to lysis by this particular mH antigen-specific CTL clone and the anti–HLA-A2 CTL clone, as compared with IL-2-stimulated normal lymphocytes and myeloid leukemias.

To determine the influence of impaired expression of adhesion molecules on the process of T-cell– mediated cytotoxicity,\(^\text{15,16}\) we investigated whether blocking of CD11a or CD18 on IL-2-stimulated normal lymphocytes would lead to decreased susceptibility to lysis by the HA-2 mH antigen-specific CTL clone (Table 4).

These results again underscore the importance of cellular adhesion molecules in the process of T-cell–mediated cytotoxicity.\(^\text{15,16}\) Alternatively, the decreased susceptibility of lymphocytic leukemic cells to CML by the HA-2 mH antigen-specific CTL clone and the HLA-A2-specific CTL clone could be caused by the physiology of the clones themselves as well as by the post-BMT donors from whom these clones were derived.

In conclusion, we have shown that circulating leukemic cells of both lymphocytic and myeloid leukemic origin are susceptible to antigen-specific HLA class I–restricted lysis by mH antigen-specific CTL clones, indicating that mH antigen-specific CTLs may play a role in the antileukemic effect of allogeneic BMT. Leukemic cells of lymphocytic origin are less susceptible to T-cell–mediated cytotoxicity by particular CTL clones as compared with IL-2-stimulated normal lymphocytes. This decreased susceptibility is not the result of impaired expression of the HLA class I molecule but may be explained by impaired expression of the LFA-1 adhesion molecule, although it cannot be ruled out that this phenomenon is caused by unique properties of the clones used.

Antirecipient mH antigen-specific reactivity can be shown in patients with and without clinical GVHD, as we have recently shown.\(^\text{15}\) Therefore, the presence of mH antigen-specific CTLs in vivo need not imply the existence of GVHD. This is in concordance with our recent observation that mH antigens are differentially expressed on keratinocytes,\(^\text{17}\) indicating that mH antigen-specific CTLs need not necessarily damage keratinocytes because the latter may lack the mH antigen recognized by these CTLs. Therefore, it is conceivable that antirecipient mH antigen-specific CTLs exert antileukemic reactivity without affecting GVHD target organs. Thus, donor-derived mH antigen-specific CTLs recognizing the recipients' leukemic cells but not normal host cells (in contrast to the clones we presently used) could possibly be applied as adjuvant immunotherapeutic agents in the treatment of leukemia.

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