**Primary Allogeneic T-Cell Responses against Mantle Cell Lymphoma Antigen-Presenting Cells for Adoptive Immunotherapy after Stem Cell Transplantation**

Mels Hoogendoorn, Judith Olde Wolbers, Willem M. Smit, M. Ronald Schaafsma, Inge Jedema, Renee M.Y. Barge, Roel Willemze, and J.H. Frederik Falkenburg

**Abstract**

**Purpose:** In patients treated with allogeneic stem cell transplantation for advanced mantle cell lymphoma (MCL), complete sustained remissions have been observed illustrating susceptibility of MCL cells to a graft-versus-lymphoma effect. To potentiate this graft-versus-lymphoma effect, adoptive transfer of in vitro selected MCL-specific CTL can be an attractive approach. The lack of expression of costimulatory molecules on MCL cells hampers the generation of MCL-reactive T-cell responses. The purpose of this study was to modify MCL cells into antigen-presenting cells (APC) and to use these MCL-APCs to induce allogeneic MCL-reactive T-cell responses.

**Experimental Design:** Interleukin (IL)-4, IL-10, CpG, and CD40 activation were tested for their capacity to up-regulate costimulatory molecules on MCL cells. Primary MCL cells or the modified MCL-APCs were then used to evaluate the induction of MCL-reactive T-cell responses in HLA-matched donors.

**Results:** Ligation of CD40 on MCL cells was essential to up-regulate costimulatory molecules and to induce production of high amounts of IL-12. In contrast to primary MCL cells, MCL-APC cells as stimulators were capable of inducing CD8⁺ CTL lines from HLA class I–matched donors. High numbers of CTL clones could be generated capable of efficiently killing the primary MCL cells and MCL-APC but not donor-specific targets.

**Conclusion:** These results show the feasibility to generate primary allogeneic T-cell responses against MCL-APC, and may provide new immunotherapeutic tools to further exploit the graft-versus-lymphoma effect following allogeneic stem cell transplantation in patients with MCL.

Mantle cell lymphoma (MCL) is a non-Hodgkin’s lymphoma, characterized by the t(11;14)(q13;q32) translocation involving the PRAD-1/bcl-1 gene resulting in overexpression of cyclin D1 (1). Patients with MCL frequently present with advanced-stage disease and have a median survival of only 3 to 4 years (2). Although in general MCL is initially responsive to conventional chemotherapy or to high-dose chemoradiotherapy followed by autologous stem cell transplantation, persistent remissions are usually not achieved reflected in the absence of a plateau phase in the survival curves (3, 4). The addition of rituximab to autologous stem cell transplantation as an in vivo purging agent or as maintenance therapy seems promising, but has not yet been definitively shown to result in a survival benefit (5–7).

Allogeneic stem cell transplantation is currently being explored as a treatment modality in patients with advanced or relapsed chemosensitive MCL. Complete sustained remissions have been observed after allogeneic stem cell transplantation, illustrating susceptibility of MCL cells to a graft-versus-lymphoma effect (5, 8). High treatment-related mortality has hampered large-scale application of allogeneic stem cell transplantation in this extensively pretreated older patient population. Reduced-intensity allogeneic stem cell transplantation has been shown to be feasible and resulted in a lower treatment-related mortality, allowing the application of nonselected donor lymphocyte infusion (9–12). However, acute and chronic graft-versus-host disease caused by alloreactive T cells present in the graft and/or in the donor lymphocyte infusion and persistence or recurrence of MCL after allogeneic stem cell transplantation has limited favorable long-term outcomes (13). Therefore, both the specificity of the immune reactivity in the context of allogeneic stem cell transplantation as well as the magnitude of the immune response specific for MCL cells have to be improved. The use of T-cell–depleted grafts avoiding the risk of graft-versus-host disease, followed by in vitro selected alloreactive T cells with specificity for the MCL cells or for hematopoiesis-restricted minor histocompatibility antigens (mHag), could be an attractive approach, and may induce complete remissions with only minor graft-versus-host disease (14).

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Transformations of mantle cell lymphoma cells into antigen-presenting cells. MCL cells were cultured in medium consisting of Iscove’s modified Dulbecco’s medium (BioWhittaker, Verviers, Belgium) with 10% fetal bovine serum. MCL cells were cultured in the presence or absence of the cytokines IL-4 and IL-10. Final concentrations of cytokines used were 1,000 units/mL (Hoffmann-La Roche, Basel, Switzerland), or in the presence of the cytokine combination IL-4 and IL-10. To trigger toll-like receptor 9, MCL cells were incubated with its ligand synthetic CpG oligodeoxynucleotide 2006 (CpG; 5’-TCGTTGTTGTTGTTGTGTGT-3’; Eurogentec, Seraing, Belgium) in the presence or absence of the cytokine combination IL-4 and IL-10. Finally, to further enhance up-regulation of costimulatory molecules, MCL cells were cocultured with IL-4 and IL-10. The expression of costimulatory molecules was verified by flow cytometry

Malignant B cells inefficiently induce allogeneic T-cell responses despite their strong expression of HLA class I and II due to inadequate expression of costimulatory and adhesion molecules (15–17). However, both normal and malignant B cells highly express CD40 molecules. Ligation of these receptors induces expression of the costimulatory molecules CD80 and CD86 and of adhesion molecules, such as CD54 and CD58, and up-regulates cytokine production (16–21). Stimulation of normal B cells can also be initiated by activating toll-like receptor 9. Toll-like receptor 9, expressed in normal and various neoplastic B cells (22–25), detects CpG motifs within bacterial DNA and has the ability to activate normal and malignant B cells (26).

Transformation of B-cell malignancies, including B-cell chronic lymphocytic leukemia, follicular lymphoma, and hairy cell leukemia, into antigen-presenting cells (APC) has been previously studied (15, 17, 20, 21, 27–29), but the modification of MCL cells into APC and the generation of MCL-reactive T-cell responses have not been reported.

In this study, we hypothesized that by transforming MCL cells into “professional” APC and using these MCL-APC to stimulate HLA-matched donor T cells, the generation of MCL-reactive CTL lines will be possible. We first examined the stimulatory capacity of cytokines, including the proinflammatory cytokine tumor necrosis factor-α and IFN-α, the B-cell–activating cytokine interleukin (IL)-4 (30), and the MCL-stimulating cytokine IL-10 (31), and the additional triggering of the toll-like receptor 9 by the synthetic agonist CpG oligodeoxynucleotide 2006 or triggering of CD40 with CD40 ligand–transfected fibroblasts (tCD40L), to up-regulate costimulatory molecules on MCL cells and to induce the production of IL-12 by these cells. Using CD40-activated MCL cells as stimulator cells, we could show that MCL-reactive mHag-specific CTL lines and clones from HLA class I–matched donors could be generated. These anti-MCL T-cell responses may be used to treat patients suffering from relapse of MCL after allogeneic stem cell transplantation.

Materials and Methods

Cell samples. After informed consent, peripheral blood samples were obtained from six patients with MCL in the leukemia phase. The diagnosis of MCL was confirmed by detection of cyclin D1 overexpression using cytohistochemical staining and verification of the t(11;14) translocation by karyotype or interphase fluorescence in situ hybridization analysis.

Table 1. Characteristic

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/age/stage</th>
<th>Phenotype</th>
<th>Cyclin D1 t (11;14)</th>
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<tr>
<td>MCL1</td>
<td>M/68/I</td>
<td>CD5+CD23−</td>
<td>+ +</td>
</tr>
<tr>
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<td>M/44/I</td>
<td>CD5+CD23−</td>
<td>+ +</td>
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<td>M/56/I</td>
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<td>F/52/I</td>
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<td>MCL6</td>
<td>M/64/I</td>
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</tr>
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</table>

Note: Cyclin D1 overexpression was detected using cytohistochemical staining. The t(11;14) translocation was verified by karyotype or fluorescence in situ hybridization analysis.

Table 2. HLA type of patients and unrelated donors

<table>
<thead>
<tr>
<th>HLA class I</th>
<th>HLA class II</th>
</tr>
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<tbody>
<tr>
<td>MCL 3</td>
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</tr>
<tr>
<td>Unrelated</td>
<td>DR17 DR16 DQ1 DQ7 DQ8</td>
</tr>
<tr>
<td>MCL 4</td>
<td>DR13* DR15 DQ6*</td>
</tr>
<tr>
<td>Unrelated</td>
<td>DR3 DR4 DQ1 DQ7</td>
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</tbody>
</table>

Note: HLA-A, HLA-B, and HLA-C typing was done by standard serology methods, and HLA-DR and HLA-DQ typing was done by DNA analysis using sequence-specific primers.

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Generation of mantle cell lymphoma–reactive CTL lines and clones. Mononuclear cells from two unrelated healthy HLA class I–matched conditions, by the counts produced by unstimulated responder cells, cells was used. All counts were corrected by subtracting the mean dinine incorporation in wells containing only responder or stimulator culture in Iscove’s modified Dulbecco’s medium with 10% human serum. IL-2 (Chirion, Amsterdam, the Netherlands) was added at different effector/target ratios ranging from 0.3:1 to 10:1. After 5 and 12 hours of incubation in a humidified atmosphere of 5% CO2 and 37°C, the wells were harvested, and to allow quantitative analysis of the cell populations, 10,000 Flow-Count fluorospheres (Coulter) were added. To stain for dead cells, propidium iodide (0.5 μg/mL) was added, then samples were properly mixed and directly analyzed by flow cytometry. For each sample, 5,000 microbeads were acquired and the absolute number of surviving cells was determined at each time point by calculation of the ratio between the number of viable cells and the number of beads. The percentage of survival was calculated as follows: % survival = [absolute number of viable CFSE− target cells (t = x)] / [absolute number of viable CFSE− target cells (t = 0)] × 100. Percentage of specific lysis was defined as 100% – % survival.

To analyze the HLA class I or II restriction of the target cell, lysis blocking studies were done. Target cells were incubated with saturating concentrations of anti–HLA class I or anti–HLA class II mAbs (W6/32 and PdV5.2, respectively) for 30 minutes before effector and target cells were cocultured. Blocking experiments at effector level were done by adding anti-CD8 mAb (FK18, RIVM, Bilthoven, the Netherlands) at a final dilution of 8 μg/mL, 30 minutes before the addition of target cells.

Statistical analysis. Statistical significance of differences was determined by paired two-tailed Student’s t test or by Wilcoxon test using the absolute values.

Results

Expression and up-regulation of adhesion and costimulatory molecules on mantle cell lymphoma cells. To determine cell surface expression of the adhesion molecules CD54 and CD58, and the costimulatory molecules CD40, CD80, CD86, and CD83, immunophenotyping of freshly isolated MCL cells from six patients was done. As shown in Table 2, the MCL cells of all patients strongly expressed HLA class II (MFIR > 50). In most patients (n = 5), a minority of the MCL cells (<45%) expressed CD54 at low levels (MFIR < 20). One patient (MCL 2) had intermediate levels (MFIR 20-50) of CD54 expression, but lacked CD58 expression. In MCL 3, almost the entire population (>80%) expressed the adhesion molecules but expression levels were low. Two of six patients showed intermediate levels of CD58. In only one patient (MCL 4), some expression of CD80 and CD83 was observed; all other MCL cases expressed no or negligible levels of CD80, CD86, and CD83. Only the costimulatory molecule CD40 was expressed by all MCL cells at intermediate levels.

In summary, in accordance with other B-cell malignancies, inadequate expression of costimulatory molecules on MCL cells was observed.
To up-regulate the expression of adhesion and costimulatory molecules on MCL cells, we first examined several cytokines, including IFN-α, TNF-α, IL-4, and IL-10. Next, activation through toll-like receptor 9 by its synthetic ligand CpG oligodeoxynucleotide 2006, in combination with the various cytokines, was tested. Finally, CD40 engagement as stimulus to modify MCL cells into APCs was analyzed in the presence of cytokines and/or CpG. Figure 1 summarizes the fluorescence-activated cell sorting analysis data of the most optimal combinations to up-regulate adhesion and costimulatory molecules on MCL cells. The data are presented as percentages of positive MCL cells (Fig. 1A) and the MFIR (Fig. 1B), and were obtained after a culture period of 96 hours. None of the tested cytokines caused any up-regulation.

CpG increased the percentage of MCL cells positive for costimulatory molecules tested, but only the expression level of CD80 was enhanced. Using flow cytometry, only weak expression of toll-like receptor 9 was observed (data not shown). Accordingly, only minor changes were observed after stimulation of MCL cells with CpG.

CD40 activation by tCD40L significantly increased the percentage of positive MCL cells for all adhesion and costimulatory molecules \((P < 0.01)\) and was superior to all combinations without CD40 stimulation. As shown in Fig. 1B, the expression levels of all these molecules, especially CD80 \((\text{MFIR} 21.3\text{-fold}, P = 0.001)\), on MCL cells were strongly up-regulated, and transformed MCL cells into characteristic APC phenotypes with high expression of CD80, CD86, and CD54. Additional stimulation with CpG or IL-10 did not further enhance the up-regulation.

To investigate the optimal time period of stimulation for full activation of MCL, phenotypic analysis of MCL cells of all six patients was done 2, 4, and 6 days after stimulation with tCD40L. As shown in Fig. 2, CD40 activation of MCL cells by tCD40L caused strong up-regulation of CD80, CD86, and CD54 within 2 days. After 4 days of stimulation, a further enhancement of expression levels of CD80 \((\text{MFIR} 2.9\text{-fold}, P = 0.01)\) and CD86 \((\text{MFIR} 3.5, P = 0.02)\) was observed. Although a significantly higher percentage of leukemic cells expressed CD83 after CD40 stimulation, the expression levels of CD83 were only minimally up-regulated. Cytospin preparations of both unstimulated and tCD40L-activated MCL cells showed that after CD40 triggering, MCL cells increased 2-fold in size and obtained a dendritic cell–like morphology with a high degree of vacuolization. In conclusion, in the absence of CD40 activation, minimal up-regulation was observed in response to IL-10 and CpG. Stimulation of MCL cells by tCD40L for a period of 4 days caused the strongest up-regulation of costimulatory and adhesion molecules, and modified MCL cells into morphologically and phenotypically characteristic APC.

To examine the functional capacity of the different MCL-APCs to produce IL-10 and IL-12, supernatants from cultures of activated MCL cells after 96 hours were measured. Whereas unstimulated MCL and CpG-activated MCL cells were not capable of producing significant amounts of IL-12 (median <15 pg/mL), high levels of IL-12 were produced by tCD40L-activated MCL cells with major variability between different patients (median 1,054 pg/mL; range 67-8,800 pg/mL; \(n = 6\)). Negligible amounts of IL-12 were produced by the CD40-activated MCL cells. Additional stimulation with CpG not only induced some increase in IL-12 production (median 1,370 pg/mL) and IL-10 (mean 14 pg/mL) were produced by the CD40-activated MCL cells. Negligible amounts of IL-12 \((\text{mean} 6\text{ pg/mL})\) and IL-10 \((\text{mean} 31\text{ pg/mL})\) but also induced the production of IL-10 \((\text{mean} 299\text{ pg/mL})\).

Mixed lymphocyte reaction using primary or mantle cell lymphoma antigen-presenting cells as stimulator cells in the presence or absence of interleukin-10 and interleukin-12. To investigate the functional significance of IL-12 or IL-10 on the stimulatory capacity of MCL cells, a mixed lymphocyte reaction was done using primary MCL cells or MCL-APC as stimulator cells and mononuclear cells from a donor as responder cells in medium with or without IL-10 or IL-12. As expected, primary MCL cells, derived from three different patients, had minimal allostimulatory capacity (see Fig. 3). IL-12 had a weak stimulatory effect on the proliferation of the allogeneic T cells, whereas IL-10 showed some inhibition of T-cell activation. In contrast, the stimulation index in response to MCL-APC as stimulators was 25 to 50, illustrating the impressive immunostimulatory capacity of these malignant APCs. As shown in Fig. 3, further increase of IL-12 concentrations did not enhance

![Fig. 1. Expression and up-regulation of costimulatory and adhesion molecules on MCL cells activated by IL-10, CpG, and/or tCD40L. MCL cells were cultured for 96 hours in the presence or absence of IL-10 (10 ng/mL), CpG (10 μg/mL), and/or tCD40L. Expression of CD80, CD86, CD54, and CD83 was analyzed by flow cytometry. MFIR was calculated as described in Materials and Methods, only if percentage of positive cells was ≥10%. Columns, mean of six patients with MCL; bars, SD. A, combinations using CD40 activation give significantly higher percentages of positive MCL cells for CD80 and CD86 \((P < 0.01)\). B, stimulation of MCL cells by tCD40L gives maximal up-regulation of expression levels of CD80 and CD86.](image-url)
T-cell proliferation nor did IL-10 suppress the induction of proliferation. In conclusion, tCD40L-activated MCL cells were considered the best MCL-APC, and were further used as stimulator cells in the subsequent experiments.

The generation of mantle cell lymphoma–reactive CTL lines and clones from HLA-matched donors. To analyze the antigen-presenting capacity of primary MCL cells and tCD40L-activated MCL (MCL-APC), T cells from a fully HLA class I–matched donor and an unrelated HLA-A– and HLA-B–matched donor were stimulated with primary MCL or MCL-APC cells. CD4 depletion was done at day 9 to eliminate allo-HLA class II responses. As shown in Fig. 4, primary MCL cells were not capable of inducing T-cell proliferation and generating T-cell lines. Although there was an HLA-C locus mismatch in the MCL 4/donor combination and although the primary MCL had some expression of CD80 and CD83 (see Table 3), this was insufficient to overcome T-cell anergy and to induce antigen-driven proliferation. In contrast, using MCL-APC cells as stimulators, vigorous expansion of CD8+ T cells was observed in both patient/donor combinations tested.

The cytotoxic activity of the CTL lines generated against MCL-APC was measured using the CFSE-based cytotoxicity assay (see Materials and Methods; ref. 35) with CFSE-labeled primary MCL cells, MCL-APC cells, and PHA blasts from the patients and donors as target cells. As illustrated in Fig. 4, the CD8+ CTL lines derived from the donors effectively killed the primary MCL cells, the MCL-APC, the PHA blasts from the patient, and not the PHA blasts from the donor in a 12-hour CFSE cytotoxicity assay. To estimate the precursor frequency of MCL-reactive T cells in the CTL lines, and to determine whether the cytotoxicity of the CTL lines was exerted by CTLs with different specificities, CTL clones were generated. In the unrelated donor α-MCL-APC 3 combination, 13% of the 1 cell/well and 8% of the 0.3 cell/well showed proliferation. Of 91 proliferating CD8+ T-cell clones, 29 showed specific lysis of primary MCL at an effector/target ratio of 10:1 (36 ± 14%, mean ± SD, n = 29) in a 12-hour CFSE cytotoxicity assay. The plating efficiency in the second combination (unrelated donor α-MCL-APC 4) was 12%, resulting in 60 of 89 CD8+ T-cell clones recognizing primary MCL cells (65 ± 20%, mean ± SD, n = 60). These results indicated that in both CTL lines, high frequencies of MCL-reactive T cells were present.

To analyze whether the MCL-reactive CTL clones were MCL, B-cell, or mHag specific, four representative clones in both patient/donor pairs were tested for cytotoxicity against MCL-specific targets, patient- and donor-derived T lymphoblasts (PHA blasts), and B-cell–specific targets [EBV-transformed lymphoblastoid B-cell lines (EBV-LCL) from patient and donor. As shown in Fig. 5, CTL clones generated from the CTL lines from both donors were reactive against MCL, MCL-APC, and EBV-LCL of the patient, and not against donor-specific targets. The clones also killed T-cell–derived targets, indicating that these T-cell clones were probably mHag specific and that the recognized mHag is not B-lineage restricted.

To confirm HLA class I–restricted recognition of the targets by the CD8+ CTL lines and clones, and to exclude HLA class II–restricted killing by contamination with CD4+ T cells, blocking studies were done using representative examples of the generated MCL-reactive CTL lines and clones. Cytotoxicity of both CTL lines was completely blocked by anti–HLA class I or anti-CD8 antibodies and not by the addition of anti–HLA class II (data not shown). Cytolytic activity of the CTL clones could partially or completely be abrogated using the anti–HLA class I antibodies (Fig. 5).
Methods.

The stimulatory capacity of the generated MCL-APC to induce vigorous allogeneic MCL-specific T-cell responses was compared with primary MCL as stimulator cell in two allogeneic donors. In the HLA-C locus mismatched setting (unrelated donor α-MCL-APC 4), the unmodified MCL cells as stimulators did not induce any antigen-driven proliferation. Although MCL-APCs were capable of provoking vigorous expansion of the donor-derived T cells and of eliciting a sustained primary allogeneic MCL-reactive immune response. These results illustrate that primary MCL cells can be adequately killed by T cells generated against MCL-APCs.

To evaluate whether MCL-specific CD8+ T-cell responses could be generated in a fully HLA class I–matched setting, mononuclear cells from the unrelated donor were stimulated with primary MCL 3 or MCL-3-APC. Again, no T-cell proliferation was observed against primary MCL 3-APC. The mixed lymphocyte reaction experiments showed that using MCL-APC as stimulator cells, an increase in IL-12 concentrations did not further enhance T-cell proliferation.

Because CD40 engagement is the major signal that induces B cells to efficiently present antigen to T cells (16, 18, 37), and because malignant B cells strongly express CD40, activation through CD40 can be an effective tool to transform tumor B cells into an antigen-presenting phenotype (15, 17, 20, 27, 28). In the present study, we show that CD40 ligation could modify MCL cells into phenotypically professional APCs with high expression of CD80, CD86, and adhesion molecules, and induced some expression of CD83. Additional stimulation through toll-like receptor 9 and cytokine receptors did not further enhance expression levels. In contrast with recent cytokine gene expression studies suggesting that both primary as well as CD40-activated MCL cells cannot produce IL-12 p40 and assemble the IL-12 heterodimer (38), we illustrated in the present study the capacity of MCL cells to synthesize IL-12. MCL cells were only capable of producing IL-12 in response to CD40 stimulation. The mixed lymphocyte reaction experiments showed that using MCL-APC as stimulator cells, an increase in IL-12 concentrations did not further enhance T-cell proliferation.

Discussion

Reduced-intensity allogeneic stem cell transplantation is considered as a new promising treatment modality for patients with advanced MCL. After allogeneic stem cell transplantation, adoptive transfer of donor T cells, capable of killing MCL cells, may eliminate residual malignant cells, resulting in long-term remissions. In this context, this experimental study was done to evaluate whether donor T cells can be triggered to preferentially kill MCL-specific targets using MCL cells as stimulator cells.

As illustrated in the results, we showed that primary MCL cells as stimulator cells failed to induce proliferation and to generate a T-cell response, even in the presence of IL-12, probably due to the lack of expression of costimulatory molecules. Thus, to generate donor T cells with high avidity for MCL cells, modification of the MCL cells into professional APC with high expression of costimulatory and adhesion molecules was hypothesized to be essential. Treatment of MCL cells with proinflammatory cytokines, B-cell activating cytokines, and with the MCL-stimulating cytokine IL-10 did not significantly induce phenotypic changes of the MCL cells. In accordance with a recent report (36), we observed limited activation of MCL cells on stimulation with CpG oligodeoxynucleotide 2006, probably due to the low expression of toll-like receptor 9 on MCL cells.
capable of eliciting mHag-specific T-cell responses, MCL-derived APC likely will skew the immune response toward recognition of MCL-specific antigens or mHags highly expressed in the MCL cells, thus leading to a more specific and efficient T-cell response.

In summary, our study shows that T-cell anergy to primary MCL cells can be reversed by transforming MCL cells into professional malignant APCs using CD40 ligation, and provides the first evidence that with the use of these MCL-APCs as stimulators, MCL-reactive mHag-specific CD8+ CTL lines and clones can be readily generated from mononuclear cells of HLA class I–matched donors. Two recent reports showed the feasibility of reduced-intensity allogeneic stem cell transplantation as salvage therapy in patients with advanced

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*Values in the table are expressed as mean fluorescence intensity ratios (MFIR), calculated as follows: Mean fluorescence intensity of cells stained with fluorochrome-conjugated antigen-specific mAbs divided by mean fluorescence intensity of cells stained with fluorochrome-conjugated isotype-control mAbs. If the percentage of positive events was <10%, MFIR of the leukemic sample was not calculated and is expressed as 0. If the percentage of positive events was ≥10%, then the MFIR is calculated and depicted as ±, ±10; +, 10-20; ++, 20-50; and ++++, 50-100.
MCL (41, 42). After allogeneic stem cell transplantation, sensible reverse transcription-PCR (RT-PCR) techniques for minimal residual disease and donor chimerism analysis enable to predict disease recurrence. The administration of donor lymphocyte infusion can lead to long-term remissions, but effectiveness may be limited due to low immunogenicity of MCL cells and the development of acute or chronic graft-versus-host disease caused by nonselected donor T cells. In this setting, the application of mHag-specific CTLs, which preferentially kill MCL cells and not nonhematopoietic targets (14), could be of great value and could prevent or treat disease recurrence after allogeneic stem cell transplantation. The magnitude and specificity of the immune response against MCL cells without causing concomitant graft-versus-host disease may be maximized.

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**References**


