Elimination of Myeloma Cells From Bone Marrow by Using Monoclonal Antibodies and Magnetic Immunobeads

By Chihiro Shimazaki, David Wisniewski, David A. Scheinberg, Jens Atzpodien, Annabel Strife, Subhash Gulati, Jerrold Fried, Rosanne Wisniewolski, Chang Yi Wang, and Bayard D. Clarkson

The efficacy of immunomagnetic beads to purge human myeloma cells from bone marrow ex vivo was evaluated. The optimal conditions for purging were studied first by using three myeloma cell lines: RPMI-8226, SKO-007, and SKMM-2. Myeloma cells labeled with the vital fluorescent dye Hoechst 33342 were admixed with normal bone marrow cells, and two monoclonal antibodies reactive with the myeloma cells (PCA-1 and BL-3) were added alone or in combination with the cells. Magnetic beads coated with goat antimouse immunoglobulin G were then added, and the tumor cells to which beads were attached were separated from the mixture with a magnet. The efficacy of tumor cell removal was dependent on the bead-to-tumor ratio; a ratio of more than 500 was optimal in the presence of excess normal marrow cells. The combination of monoclonal antibodies PCA-1 and BL-3 increased the tumor cell removal as compared with either antibody alone. Two cycles of treatment were more effective than one cycle was. Under optimal conditions, 2.3 to 4 logs of tumor cells could be removed from the mixture containing 10% myeloma cells without a significant loss of normal hematopoietic progenitors as measured by CFU-GM, CFU-GEM, and BFU-E. When the efficacy of this procedure was tested on fresh bone marrow from patients with multiple myeloma (MM) by using the combination of PCA-1, BL-3, and J-5, 1.6 to 2.5 logs of tumor cells could be removed by one cycle of treatment, even from marrows containing less than 10% myeloma cells. These observations support the use of monoclonal antibody combinations and immunobeads as a reliable and nontoxic method to eliminate contaminating myeloma cells ex vivo in preparation for autologous bone marrow transplantation in patients with MM.

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banks of the Laboratory of Human Cancer Immunology, Sloan-Kettering Institute. SKMM-2 and SKMM-1 were established from patients with plasma cell leukemia and were kindly provided by Dr A. Houghton (O. Eton, D.A. Scheinberg, A.N. Houghton, submitted).

These cell lines were cultured in RPMI 1640 medium supplemented with 15% FCS, 1% penicillin-streptomycin-neomycin antibiotics (GIBCO, Grand Island, NY), and 1% l-glutamine and maintained under exponential growth conditions at 37°C in a humidified atmosphere of 5% CO₂ in air.

Monoclonal antibodies. Three monoclonal antibodies were used in this study. Anti-PCA-1 (obtained from Coulter Immunology, Hialeah, FL) recognizes plasma cell-associated antigens on myeloma, plasma cell leukemia, and plasmacytoma tumor cells. This antigen is also weakly expressed on granulocytes and monocytes. Anti-BL-3 recognizes 105-kilodalton (Kd) antigen that is expressed on plasma cells and late-stage cells of B-cell differentiation and is reactive with normal bone marrow cells. Anti-J-5 (CD10) (obtained from Coulter Immunology) recognizes 100-Kd antigen (CALLA) that is expressed on 80% of non-B, non-T acute lymphoblastic leukemia and a small population of normal bone marrow lymphoid cells. This antigen is also expressed on normal fibroblasts and granulocytes but is not detected on normal hematopoietic progenitors. Recently, this antigen has been reported to be present on myeloma cells in some aggressive cases and on the progenitor cells of MM.

Determination of antibody binding to myeloma cells. One million cells in RPMI 1640 medium with 5% heat-inactivated FCS (HIFCS) and 0.1% sodium azide were reacted with the monoclonal antibody in a final volume of 0.2 mL on ice for 30 minutes, washed twice with phosphate-buffered saline (PBS) containing 2% HIFCS and 0.1% sodium azide (rinsing medium), and then reacted with fluorescein isothiocyanate (FITC)-conjugated sheep antimouse immunoglobulin, F(ab')₂ fragments (Cooper Biomedical, Malvern, PA) on ice for 30 minutes. Cells were then washed twice and analyzed by flow cytometry. Control samples were stained with purified nonspecific mouse immunoglobulins of the same isotype (Coulter Immunology). Cells were analyzed by using a FACS IV flow cytometer (Becton Dickinson, Mountain View, CA) with excitation at 488 nm. Forward and 90° light scatter signals were used as gates either to exclude dead cells and debris (cell lines) or to select plasma cells for analysis (myeloma bone marrow). Data were analyzed at the SKI Core Computer Facility by using a PDP 11/70 computer.

All experiments were performed at least three times. Immunomagnetic purging method on cell lines. The efficacy of immunomagnetic purging was examined on tumor cells alone and normal bone marrow containing various percentages of contaminating tumor cells. Uniform magnetic polystyrene beads (M-450) coated with goat antimouse IgG and a magnetic particle concentrator (MPC-1) were purchased from Dynal Inc (Fort Lee, NJ). The beads were washed twice and suspended in 0.2 mL of rinsing medium before use.

When the tumor cells alone were treated, 0.4 × 10⁶ cells were stained with a saturating concentration of PCA-1 that was determined by flow cytometry. After washing, the cells were suspended in 0.1 mL of rinsing medium, mixed with 0.2 mL of beads coated with antimouse IgG, and incubated on ice for one hour, with mixing every 5 minutes. The sample was then diluted to 3 mL with RPMI 1640 medium containing 10% FCS, and the cells to which beads were attached were isolated from the unreactive cells by placing the tube on the MPC. After three minutes, the suspension was aspirated, and cells in the aspirate were counted.

To simulate ex vivo bone marrow purging conditions, various numbers of cultured myeloma cells, which were marked in advance with the supravital DNA stain H342 (Calbiochem-Behring Corp, La Jolla, CA), were mixed with normal bone marrow cells. Two million cells from the mixtures were incubated with each monoclonal antibody or antibody combination, washed and mixed with beads, and then separated by using the magnet as described earlier. After treatment, cells that were not separated were stained with 0.1% trypan blue, and the total number of cells remaining and the viable fluorescent cells were counted by using a Leitz fluorescence microscope with UV excitation. The number of cells removed was calculated from the number of H342-stained cells before and after purging.

Effect of immunomagnetic purging on fresh myeloma cells. Two million bone marrow mononuclear cells from each patient were stained with the monoclonal antibody combination (PCA-1, BL-3, and J-5), washed, incubated with beads at a bead-to-total cell ratio of 100 (the bead-to-myeloma cell ratio varied from 130 to 3,700:1), and then separated with a magnet as described earlier. Smears were made before and after the treatment and stained with May-Grünwald-Giemsa for morphologic determination. Additional smears were fixed with methanol/acetone at 4°C for 30 minutes and stained for cytoplasmic immunoglobulin with FITC-conjugated goat F(ab')₂, antihuman heavy- and light-chain antibodies (Tago, Inc, Burlingame, CA). Slides were washed with PBS, mounted, and examined by fluorescence microscopy for the detection of residual myeloma cells.

Effect of immunomagnetic purging on normal hematopoietic precursors. Two million bone marrow mononuclear cells from a healthy donor were processed with immunomagnetic beads by following the same procedures described earlier. After treatment, the cells were assayed for colonies derived from CFU-GM, CFU-GEM, and BFU-E as described previously.

Briefly, cell cultures consisted of 1 mL of Iscove's modified Dulbecco's medium (GIBCO) containing 24% FCS, 0.8% deionized bovine serum albumin (Sigma Chemical Co, St Louis), 10⁻⁴ mol/L of 2-mercaptoethanol (Sigma), 1 unit of partially purified human urinary erythropoietin (Toyobo, Inc, New York) and methylcellulose at a final concentration of 1.3% in 35-mm Lux tissue culture dishes (Miles Scientific, Naperville, IL). Quadruplicate cultures were incubated in a humidified atmosphere of 5% CO₂ in air. CFU-GM, CFU-GEM, and BFU-E were counted on day 14.

RESULTS

Reactivity of monoclonal antibodies to myeloma cell lines. Reactivity of each monoclonal antibody to five myeloma cell lines is shown in Table 1. PCA-1 reacted with three of the five cell lines, and BL-3 reacted with all five, although two cell lines were weakly positive. J-5 reacted with three of the cell lines, but two of these were weakly positive. Saturation of binding was achieved at 12.5 μg/mL with PCA-1, 25 μg/mL with BL-3, and 50 μg/mL for J-5.

On the basis of these observations, RPMI-8226, SKO-007, and SKMM-2 were selected for further model experiments to assess the efficacy of immunomagnetic purging. When these three cell lines were stained with the combination of monoclonal antibodies PCA-1 and BL-3, the fluorescence intensities were increased, and the percentages of positive
from the mixture of tumor cells with normal bone marrow cells. To examine whether the same effect was obtained in these three cell lines.

**Immunomagnetic purging of unmixed tumor cell population.** The number of beads required for maximum removal of tumor cells was first optimized (Table 2). On the basis of these data, a bead-to-tumor ratio of 100 was used for further experiments using unmixed tumor cells.

The effects of immunomagnetic purging on the three tumor cell lines were examined by using a saturating concentration of PCA-i and a bead-to-tumor ratio of 100. Seventy-two percent to 97% of the cells were removed (Fig 1). Control depletion was less than 15%. The percentages of cells removed were virtually identical to the number of positive cells determined by FACS analysis (Table 1) on each cell line. This suggests that this procedure is extremely efficacious and capable of removing cells expressing only a few antigen molecules.

**Effect of immunomagnetic purging on tumor cell removal from the mixture of tumor cells with normal bone marrow cells.** To examine whether the same effect was obtained in the presence of normal bone marrow cells, mixtures of RPMI-8226 cells with normal bone marrow cells were treated with a combination of PCA-i and BL-3 (Table 3). With a bead-to-total cell ratio of 10, the efficacy of removal decreased with increasing percentages of tumor cells in the mixture, and only 1 log of tumor cells was removed from the suspension containing more than 50% tumor cells. These findings suggested that the efficacy of purging was dependent on the bead-to-tumor cell ratio. With a bead-to-tumor ratio of 100, 2.1 and 2.6 logs of tumor cells were removed from the mixture containing 1% and 10% tumor cells, respectively. With a bead-to-tumor ratio of 500 or greater, the efficacy appeared to be independent of the concentration of tumor cells, and about 3 logs of tumor cells could be removed from the mixtures containing 10% and 1% tumor cells. Therefore, a bead-to-tumor ratio of 1,000 was selected for further model experiments on the mixture of 10% tumor cells.

To simulate ex vivo bone marrow purging conditions, normal bone marrow cells were mixed with H342-stained myeloma cells to a 10% total contamination (Table 4). More than 2 logs of RPMI-8226 cells could be removed with PCA-i or BL-3 alone, and 3.2 logs of tumor cells could be removed by both antibodies together (Table 4). Similar effects by the combination were seen on the other cell lines (data not shown). These effects of the combination of monoclonal antibodies were in accordance with the observations by flow cytometry that the combination of monoclonal antibodies increased the fluorescence intensity and the percentage of positive cells. Two cycles of treatment were more effective than one (Table 4, Fig 2), with 2.3 and 4 logs depletion achieved.

**Effect of immunomagnetic purging on removal of fresh myeloma cells.** To assess the efficacy of the one-cycle procedure on the removal of fresh myeloma cells, four fresh myeloma marrows containing various percentages of

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**Table 1. Reactivities of Monoclonal Antibodies Against Five Myeloma Cell Lines**

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Percentage of Cells Positive* (PK/PK,%)</th>
<th>PCA-1</th>
<th>BL-3</th>
<th>PCA-1 + BL-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SK-RCS-1</td>
<td>96 ± 1 (2.5)</td>
<td>0 ± 0 (1.0)</td>
<td>27 ± 6 (1.2)</td>
<td>ND</td>
</tr>
<tr>
<td>RPMI-8226</td>
<td>36 ± 7 (1.3)</td>
<td>97 ± 1 (3.9)</td>
<td>97 ± 1 (3.9)</td>
<td>98 ± 2 (4.6)</td>
</tr>
<tr>
<td>SKO-007</td>
<td>8 ± 6 (1.1)</td>
<td>69 ± 8 (2.1)</td>
<td>98 ± 3 (3.8)</td>
<td>100 ± 0 (3.7)</td>
</tr>
<tr>
<td>SKMM-2</td>
<td>25 ± 5 (1.2)</td>
<td>78 ± 5 (2.4)</td>
<td>92 ± 5 (2.6)</td>
<td>97 ± 2 (3.1)</td>
</tr>
<tr>
<td>SKMM-1</td>
<td>7 ± 0 (1.0)</td>
<td>0 ± 0 (1.0)</td>
<td>34 ± 1 (1.3)</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviation: ND, not done.

*Mean ± SD.

†Peak fluorescence of sample divided by peak fluorescence of control.

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**Table 2. Effect of Bead-to-Tumor Cell Ratio on the Removal of Unmixed Tumor Cells**

<table>
<thead>
<tr>
<th>Bead-to-Tumor Cell Ratio</th>
<th>Log Tumor Cells Removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1.0</td>
</tr>
<tr>
<td>50</td>
<td>1.7</td>
</tr>
<tr>
<td>100</td>
<td>1.5</td>
</tr>
<tr>
<td>200</td>
<td>1.6</td>
</tr>
</tbody>
</table>

RPMI-8226 cells were treated with PCA-i and then mixed with magnetic beads and separated by magnet. The numbers of cells before and after treatment were counted, and the log tumor cells removed were calculated.

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**Fig 1.** Three myeloma cell lines were incubated with PCA-1 (III) or mouse IgG2a (III), mixed with beads coated with goat antimouse IgG, and then separated by means of a magnetic field. In one experiment, the same procedures were performed without antibody and beads as a control (III). The recoveries of cells after treatments without antibody and beads were more than 92% in each line, and those after treatment with mouse IgG2a were more than 85%. The recoveries of RPMI-8226, SKO-007, and SKMM-2 after treatment with PCA-1 were 3%, 28%, and 16%, respectively. Values are represented as means ± SD (n = 2).
myeloma cells were treated with the monoclonal antibody combination of PCA-1, BL-3, and J-5 (Table 5). Cytoplasmic immunoglobulin staining of myeloma cells with a sensitivity of one cell in 1,000 cells was used to detect residual myeloma cells. Myeloma cells at 1.6 to 1.7 logs were removed from the marrow even in cases with less than 10% myeloma cells (patients 3 and 4). In the patient with a low reactivity of fresh myeloma cells to PCA-1 and J-5 (patient 1), 2.5 logs of myeloma cells were removed, which suggests the utility of the monoclonal antibody combination to overcome antigen heterogeneity.

Effect of immunomagnetic purging on normal hematopoietic progenitors. The numbers of CFU-GM, BFU-E, and CFU-GEM recovered after treatment with PCA-1 or BL-3 were unchanged after treatment, thus demonstrating that these antibodies were unreactive with normal hematopoietic precursors (Table 6).

**DISCUSSION**

This report describes the purging of myeloma cells from bone marrow ex vivo by using monoclonal antibodies and immunomagnetic beads. Currently, C' cytotoxicity with specific monoclonal antibodies is the method most extensively used for the removal of contaminating tumor cells from autografts. However, this method has major drawbacks related to the C' as well as being limited to use with C'-fixing antibodies as described earlier. Toxins conjugated to monoclonal antibodies have also been developed and widely used. However, this method requires that the toxin be internalized into the cytoplasm, a condition not always met in many antigen-antibody systems. Recently the selective removal of tumor cells by using immunomagnetic beads has provided an alternative approach and makes possible the use of a wide variety of monoclonal antibodies that do not fix C' (eg, BL-3, an immunoglobulin of subclass IgG1). Moreover, since the action of the beads requires only surface binding of the monoclonal antibodies, internalization of the antigen is not a limitation. Finally, the separation procedures are done at 4°C, which reduces the problems associated with modulation.

Several monoclonal antibodies that react with myeloma or normal plasma cells have been described. PCA-1 is an IgM antibody specific to plasma cells. Although we do not bind to IgG, this antibody could be used with C' or with beads coated with an anti-IgM antibody. Rl-3 reacts only with a subset of plasma cells and lymphocytes. MM-4 is another IgG1 antibody specific for plasma cells that we plan to use in future experiments. PCA-1 is not specific to plasma cells and is weakly expressed on granulocytes and monocytes but not on CFU-GM. BL-3 reacts with the later stages of B-cell differentiation. On the basis of our analyses of cell surface markers of myeloma bone marrow as well as myeloma cell lines, we selected BL-3,

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**Table 3. Effect of Bead-to-Tumor Cell Ratio on the Removal of RPMI-8226 Cells From the Mixture With Normal Bone Marrow Cells**

<table>
<thead>
<tr>
<th>Percentage of Tumor Cells in Mixture</th>
<th>Bead-to-Tumor Cell Ratio</th>
<th>Log Tumor Cells Removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>1,000</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>100</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>500</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
<td>1,000</td>
</tr>
<tr>
<td>10</td>
<td>200</td>
<td>2,000</td>
</tr>
</tbody>
</table>

H342-stained RPMI-8226 cells were mixed with normal bone marrow cells, treated with the combination of monoclonal antibodies PCA-1 and BL-3, mixed with beads, and separated by magnet. The log tumor cells removed was calculated by the number of H342-stained cells before and after treatment.

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**Table 4. Removal of RPMI-8226 Cells From Bone Marrow Containing 10% Tumor Cells**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Log Tumor Cells Removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCA-1</td>
<td>2.7</td>
</tr>
<tr>
<td>BL-3</td>
<td>2.1</td>
</tr>
<tr>
<td>PCA-1 + BL-3</td>
<td>3.2</td>
</tr>
<tr>
<td>PCA-1 + BL-3 (2 cycles)</td>
<td>4.0</td>
</tr>
</tbody>
</table>

H342-stained RPMI-8226 cells were mixed with normal bone marrow cells and treated as described in Table 3.
Two million bone marrow cells from myeloma patients were treated with the combination of monoclonal antibodies (PCA-1, BL-3, and J-5), mixed with treated beads, and then separated by magnet. Smears were made before and after treatment and stained with antihuman heavy and light chains. Cytoplasmic immunoglobulin-positive and -negative cells were counted, and the percentages of recovery and log plasma cells removed were calculated.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Percentage of PC (after)</th>
<th>RTC (%)</th>
<th>RPC (%)</th>
<th>Log PC Removed</th>
<th>Percentage of Myeloma Cells Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77.3</td>
<td>3.2</td>
<td>7.0</td>
<td>0.29</td>
<td>PCA-1: 15, BL-3: 85, J-5: 0</td>
</tr>
<tr>
<td>2</td>
<td>45.3</td>
<td>2.6</td>
<td>33.5</td>
<td>1.92</td>
<td>PCA-1: 58, BL-3: 94, J-5: 19</td>
</tr>
<tr>
<td>3</td>
<td>7.6</td>
<td>0.47</td>
<td>41.5</td>
<td>2.57</td>
<td>PCA-1: 19, BL-3: 30, J-5: 8</td>
</tr>
<tr>
<td>4</td>
<td>2.7</td>
<td>0.1</td>
<td>48.5</td>
<td>1.80</td>
<td>PCA-1: 90, BL-3: 80, J-5: 35</td>
</tr>
</tbody>
</table>

Abbreviations: PC, plasma cells; RTC, recovery of total cells; RPC, recovery of plasma cells.

*RPC (%) = percentage of PC (after) x RTC (%) /percentage of PC (before).

Table 6. Recovery of Hematopoietic Precursors After Treatment with Immunobeads

<table>
<thead>
<tr>
<th>RTC (%)</th>
<th>Cloning Efficiency</th>
<th>Percent Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CFU-GM</td>
<td>BFU-E</td>
</tr>
<tr>
<td>Malig</td>
<td>58</td>
<td>0.118</td>
</tr>
<tr>
<td>PCA-1</td>
<td>54</td>
<td>0.129</td>
</tr>
<tr>
<td>BL-3</td>
<td>54</td>
<td>0.130</td>
</tr>
</tbody>
</table>
possible explanation for this observation is that the higher bead-to-tumor ratio used in the present study made it possible to remove tumor cells expressing a few antigen molecules on the cell surface in the first cycle of treatment.

Under optimal conditions, 2.3 to 4 logs of myeloma cells could be removed by the procedure presented here. Dickie et al.\(^9\) reported that a 6-log reduction would be necessary to completely remove tumor cells ex vivo. Therefore, an additional 2- to 3-log removal is presumably required. Recently, San Miguel et al.\(^10\) reported that most myeloma cells reacted with FMC-8 (CD-9), and preliminary unpublished studies in our laboratory showed that BA-2 (CD-9) was highly expressed on myeloma cells. This antibody mediates C\(^+\) dependent cytolysis, and LeBien et al.\(^11\) have used BA-2 and C\(^+\) for purging of leukemia cells. Combinations of immunomagnetic purging with C\(^+\)-mediated cytolysis by BA-2 might increase the reduction of tumor cells sufficiently to allow BMT. These studies are currently under investigation.

Combinations of nonimmunologic methods with the use of immunomagnetic beads might also be effective against cells that were not removed by antibody and complement. De Fabritiis et al.\(^12\) reported that 6 logs of Burkitt's cells could be removed with 4-hydroperoxycyclophosphamide (4-HC) in combination with monoclonal antibodies and C\(^+\). Uckun et al.\(^13\) reported that the combination of 4-HC with immuno-toxin was superior to either 4-HC or immunotoxin alone. We have already demonstrated that more than 4 logs of myeloma cells growing in culture could be killed at the concentration of 60 \(\text{nmol}\)/L of 4-HC, a dose level that does not inhibit engraftment.\(^13\) This suggests that the combination of immunomagnetic purging with 4-HC is another possible approach.

For successful autologous BMT, tumor cells must be removed not only from bone marrow harvested ex vivo but also from the patient during ablative therapy. In this context, the treatment of MM patients by using high-dose melphalan is encouraging.\(^14\) Autologous BMT prevents serious infections associated with high-dose melphalan.\(^4\) The European Cooperative Group for BMT reported that five of 15 patients treated with high-dose cyclophosphamide and total-body irradiation followed by allogeneic BMT from HLA-compatible sibling donors were well, without signs of active disease.\(^12\) Therefore, high-dose chemotherapy in combination with purged autologous BMT might be useful as a new therapeuetic modality for patients with MM.

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Elimination of myeloma cells from bone marrow by using monoclonal antibodies and magnetic immunobeads

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