Idiotypic Protein-pulsed Adherent Peripheral Blood Mononuclear Cell-derived Dendritic Cells Prime Immune System in Multiple Myeloma

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ABSTRACT
Adherent peripheral blood mononuclear cell-derived dendritic cells pulsed with autologous idiotypic protein (Id) were given to a patient with advanced-stage refractory myeloma. Potentially beneficial antmyeloma Id-specific immune responses were produced, characterized by MHC-dependent T-cell-proliferative responses with cytokine release and the production of anti-Id antibodies. A T-cell line generated after vaccination was also able to lyse autologous Id-pulsed targets and recognize fresh autologous myeloma cells. The immune responses were associated with a transient minor fall in the serum Id level and were not ablated by high-dose myeloablative chemotherapy. This report therefore demonstrates the clinical use of adherent peripheral blood mononuclear cell-derived dendritic cells for vaccination in cancer and the persistence of immune responses after high-dose chemotherapy. Such a therapeutic approach may be useful in reducing the relapse rate in patients who have minimal residual disease after chemotherapy.

INTRODUCTION
Multiple myeloma is a B-cell malignancy originating from an early B lymphocyte that proliferates and differentiates to the end-stage myeloma plasma cell (1, 2). Although it is possible to produce a period of disease remission using combination chemotherapy, most patients with myeloma eventually relapse and die of the disease. Allogeneic bone marrow transplantation may cure the disease, but most patients with multiple myeloma are too old for such an intensive procedure. Therefore, novel therapeutic strategies aimed at reducing the disease relapse rate are much needed.

T cells are potent cellular effectors of the immune system. They possess memory and can respond to rechallenge by the same antigen. If a tumor-specific antigen could be targeted to produce an antmyeloma effect, immunotherapy would seem to be an ideal therapeutic approach. Active myeloma could be induced into remission using chemotherapy, and disease relapse could be prevented by long-term tumor immunosurveillance provided by memory T cells.

The malignant cells in myeloma undergo immunoglobulin gene rearrangement and produce paraprotein (Id). Id produced by myeloma plasma cells is secreted into the serum, and the malignant cells express very little surface Id. Id is clone specific and may be a suitable tumor antigen for immune targeting.

However, the ability to generate a strong and uniform antitumor immune response depends on a few factors. Whereas the nature of the antigen may be an important consideration, the optimal and effective processing and presentation of antigens to the immune system is also paramount. DCs are powerful antigen-presenting cells equipped with the necessary costimulatory molecules needed for the initiation of an effective primary immune response (3, 4). Animal studies have demonstrated that DCs pulsed with tumor peptides can be used to induce protective immunity against tumor challenge (5). Clinical responses have also been observed in four B-cell lymphoma patients treated with DCs pulsed with the lymphoma Id (6). DCs can be expanded in vitro from CD34+ cells (7-9). However, the number of circulating CD34+ cells in the peripheral blood in the stable state is extremely low. Therefore, most protocols for the generation of DCs have involved the administration of chemotherapy followed by granulocyte colony-stimulating factor or GM-CSF, so that large numbers of CD34+ progenitor cells can be collected from the peripheral blood during bone marrow regeneration. Although DCs can be generated by a simpler method using adherent PBMCs with a combination of GM-CSF and IL-4 (10, 11) with or without tumor necrosis factor α, it remains unclear whether DCs thus generated are able to uptake, process, and present antigen efficiently. Furthermore, DCs generated from adherent PBMCs are unstable and revert back to macrophage/monocyte phenotypes a few days after withdrawal of the cytokines. In this report, however, we demonstrate that adherent PBMC-derived DCs are able to function adequately in vivo to present myeloma Id to a patient with refractory advanced...
myeloma, with the subsequent generation of Id-specific immune responses that have an antimyeloma effect.

MATERIALS AND METHODS

Isolation of Id. To isolate and purify the myeloma Id from serum, we used DEAE chromatography. The protein was more than 95% pure as determined by SDS-polyacrylamide gel electrophoresis. A control Id was also isolated using the same methodology from the serum of another patient with an IgGκ multiple myeloma with a similar level of immune-peresis. This control Id was included in subsequent experiments to determine the specificity of the immune responses.

DC Generation. The patient underwent leukapheresis to enable the harvesting of a large number of PBMCs. Fresh PBMCs were prepared by Ficoll-Hypaque centrifugation, washed, and resuspended in RPMI 1640 and 10% FCS. PBMCs were incubated at 37°C in 5% CO₂ for 2 h. Nonadherent cells were removed by gentle washes. The adherent cells were then cultured in RPMI 1640 and 10% FCS supplemented with GM-CSF (800 units/ml) and IL-4 (500 units/ml) for 7 days. The cells were pulsed with Id (200 μg/ml) and KLH (50 μg/ml) on days 1 and 6 of culture.

Proliferation Assays. Fresh PBMCs were seeded in 96-well flat-bottom microtiter plates (Becton Dickinson, San Jose, CA) at 2 × 10⁵ cells/well in 100 or 200 μl of RPMI 1640 supplemented with 10% FCS, 1 mM glutamine, 100 units/ml penicillin, 100 μg/ml streptomycin, and 25 mM HEPES (referred to henceforth as complete medium). KLH, Id, or an isotype control Id was added to cultures in various final concentrations, and the cultures were incubated at 37°C in 5% CO₂. Cells were pulsed on day 4 with 0.5 μCi of [methyl-³H]thymidine/well and harvested 18 h later. [methyl-³H]Thymidine incorporation was measured by liquid scintillation counting. Results from triplicate cultures are given as the arithmetic means ± SD. For blocking assays, dialysed anti-MHC class I (Sera-Lab, Porton Down, United Kingdom) and anti-HLA-DR (Dakopatts, Glostrup, Denmark) antibodies were added to a final concentration of 20 μg/ml. A control antibody, a mouse antihuman CD33 antibody, which was treated similarly, was also used. Supernatants were harvested after 72 h and assayed for the production of IFN-γ using a commercially available ELISA kit (Genzyme, Cambridge, MA). All results were confirmed on at least two separate occasions.

Generation of T-Cell Lines. PBMCs obtained after completion of all vaccinations were incubated in complete medium in 50-ml tissue culture flasks at 37°C in 5% CO₂. The cells were stimulated weekly with Id (40 μg/ml) and recombinant IL-2 (40 units/ml) and every 2 weeks with autologous irradiated (4000 rads) PBMCs. The cells were used weekly in a coculture system for the measurement of T-cell proliferation and the production of IFN-γ in the supernatant and Id-specific CTLs. Control T cells consisted of PBMCs obtained from the same patient before vaccination and propagated by IL-2 (40 units/ml) and biweekly autologous irradiated PBMCs.

CTL Assays. The CTL precursor assay was carried out using a modified in-house protocol previously designed to detect alloreactive CTL precursors against recipient cells in marrow donors in the transplant setting. Briefly, PBMCs obtained before and weekly after each vaccination were incubated in 96-well round-bottom microtiter plates at 2 × 10⁵ cells/well in a volume of 150 μl of complete medium in the presence of Id (50 μg/ml) and IL-2 (30 units/ml) for 1 week. The cells were then assayed for their cytotoxic ability for various targets in a standard 4-h ⁵¹Cr release assay. Target cells were CD3-depleted antigen-loaded autologous PBMCs. Target cells were labeled with Na₂⁵¹CrO₄ for 1 h and mixed with precultured effector cells. All assays were performed in triplicate and confirmed on three separate occasions. Results are shown as the mean percentage of ⁵¹Cr release, calculated as follows:

\[
\% \text{ Release} = \frac{(\text{sample counts} - \text{spontaneous counts})}{(\text{maximum counts} - \text{spontaneous counts})} \times 100\%
\]

ELISA Measurements of Antibodies. Antibody responses to vaccination were measured by ELISA. The microtiter plates were coated with Id, an isotype control Id, or KLH (at 50 μg/ml) overnight. Pre- and postvaccination serum samples were serially diluted and allowed to bind to the target proteins. The binding of anti-Id IgM antibodies and anti-KLH IgM antibodies was detected by mouse antihuman IgM antibodies, followed by horseradish peroxidase-conjugated goat antimouse IgG antibodies. The binding of anti-KLH IgG antibodies was detected using biotinylated goat antihuman IgG antibodies, followed by peroxidase-conjugated streptavidin.

RESULTS

Vaccination. A 43-year-old man presented in March 1996 with IgGκ myeloma. His clinical characteristics are shown in Table 1. At presentation, he had mild hypercalcemia but normal renal function. The serum β₂-microglobulin level was 4.4 mg/l, indicating that he belonged to the group of patients with a poor prognosis. He received various chemotherapy regimens before vaccination, and the best paraprotein response to each regimen is shown in Table 1. The interval between the last course of chemotherapy (miniBEAM) and the first DC vaccination was 6 weeks. DCs were successfully generated from adherent PBMCs after 7 days of culture and confirmed by immunophenotyping showing that at least 20% of the cells were CD1a+, CD11c+, CD80+, CD86+, and HLA-DR+. They were also CD3−, CD8−, and CD14−. The cells were pulsed with both Id and a control vaccine, KLH, on days 1 and 6 of the 7-day culture.

The patient received three antigen-pulsed DC vaccinations, each given every 14 days. The DCs were washed and resuspended in 10% human albumin solution before i.v. infusion, and the number of cells reinfused on each occasion was 5 × 10⁸, 30 × 10⁶, and 45 × 10⁶ cells, respectively. Each vaccination was given with an i.v. antihistamine, chlorpheniramine (10 mg). All three vaccinations were well tolerated without any side effects.

Immunological Responses. PBMCs were obtained from the patient immediately before and weekly after vaccination. Before vaccination, T cells did not show any proliferation to in

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4 Lim et al., unpublished observations.
vitro challenge with Id (Fig. 1a). After vaccination, KLH-specific T-cell proliferation not present before vaccination was repeatedly observed (Table 2), indicating that DCs generated from adherent PBMCs were able to uptake, process, and present exogenously loaded antigen to prime T cells in vivo. This also confirms the ability of the immune system to respond to a vaccine given via DCs, even in a patient with an active advanced-stage malignant disease who had recently been exposed to high-dose chemotherapy. Similarly, Id-specific T-cell-proliferative responses were reproducibly observed after the first vaccination, and the proliferative responses increased progressively with successive rounds of vaccination. The proliferative responses were Id specific and did not occur when an isotype control Id was used to challenge the T cells (Fig. 1a). Furthermore, Id consistently induced the production of IFN-γ by T cells in a dose-related manner (Fig. 1b). The proliferative (Fig. 1c) and cytokine (Fig. 1d) responses could be reproducibly blocked by antibodies directed at both MHC class I and class II molecules but not by the isotype control CD33 antibody, suggesting that recognition of Id T-cell epitopes was mediated through the MHC molecules. The blocking was observed predominantly with HLA-class II antibodies. These results therefore indicate the successful induction of MHC-dependent Id-specific T-cell responses in advanced-stage myeloma after vaccination with antigen-pulsed adherent PBMC-derived DCs.

Using a CTL detection protocol, however, we were unable to detect any CTL response to Id-pulsed CD3-depleted autologous PBMCs in any of the fresh peripheral blood T lymphocytes taken from the patient after the three courses of DC vaccination (data not shown). Despite this, a T-cell line generated from PBMCs taken after vaccination was able to kill Id-pulsed CD3-depleted autologous PBMCs after seven rounds of in vitro Id restimulation (Fig. 2). This level of cytotoxicity was observed repeatedly on three separate experiments. In contrast, T cells propagated using IL-2 only did not do so. Therefore, the Id-specific T-cell line was able to lyse Id-pulsed targets in an Id-dependent manner, but the Id specificity of the lysis is not established in these experiments. It is likely that CTLs could potentially have been induced in vivo, but the CTL frequency in the blood might have been too low to be detected by our CTL detection protocol. Additional rounds of vaccination may increase the Id-specific CTL frequency in the peripheral blood.

To determine whether the T-cell line generated from repeated rounds of Id stimulation was able to recognize autologous myeloma cells, the T cells were cocultured with fresh autologous irradiated myeloma cells. Id-primed T cells showed a strong proliferative response not seen when IL-2-propagated T cells were used as the responder cells in the coculture system (Fig. 3), suggesting the presence of T-cell epitopes on the myeloma cell surface that have been derived from autologous Id. In contrast to T cells propagated using only low-dose IL-2, the T-cell line primed with repeated rounds of Id showed a higher proportion of CD4 T cells expressing both CD25 and HLA-DR surface markers (Table 3).

The vaccination strategy we adopted also produced B-cell responses. Both anti-KLH IgM and IgG antibodies were detected in the serum after vaccinations, with IgM reaching a peak level between weeks 2 and 3, and IgG reaching a peak level on week 5 (Table 2). Despite the persistence of a high level of circulating Id, we were also able to repeatedly detect the presence of specific anti-Id IgM antibodies in the serum (Fig. 4). This was surprising in the face of a high circulating Id level and probably indicates that the IgM was of low affinity and thermal range, so that binding to Id improved in vitro, at a lower temperature, than in vivo.

**Disease Response.** Disease response to vaccine was monitored by weekly measurements of serum Id levels. Before DC vaccination, the disease was progressing rapidly over a 6-week period, from a post-minibeam level of 31 g/l to a prevaccination level of 41 g/l. A minor but definite transient reduction in Id levels was observed after the first vaccination. Serum Id level dropped to 35 g/l. However, the disease rapidly escaped and progressed, despite two additional rounds of DC vaccination. The Id levels increased again and reached a maximum of 47 g/l 5 weeks after the first vaccination. As a result, the patient received high-dose melphalan (200 mg/m²) with peripheral blood stem cell support. He responded to the high-dose melphalan and achieved a good partial remission. He is not now (8+ months after high-dose Melphalan) on any specific medication and is well with minimal symptoms. His serum Id levels run around 12 g/l.

**Id-specific Immunity after High-Dose Melphalan.**

Two months after the high-dose melphalan, peripheral blood lymphocytes were reassessed for Id-specific immunity. Despite the high-dose myeloablative chemotherapy, Id-specific T cells remained detectable in the peripheral blood. Fresh PBMCs showed dose-dependent proliferative responses (Fig. 1a) and IFN-γ production (Fig. 1b) when challenged in vitro with Id. Therefore, these results demonstrate that a strong memory T-cell response could be induced in advanced-stage myeloma using

Table 1  Patient’s characteristics

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>43</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Presentation serum Id level</td>
<td>60 g/l</td>
</tr>
<tr>
<td>Id isotype</td>
<td>IgG k</td>
</tr>
<tr>
<td>Presentation β2-microglobulin level</td>
<td>4.4 mg/l</td>
</tr>
<tr>
<td>Presentation bony lesions</td>
<td>Large lytic lesion in left inferior pelvic ramus</td>
</tr>
<tr>
<td>Prior chemotherapy and maximum reduction in serum Id levels</td>
<td>VAD* X 5 courses, 50% Id reduction; HDC+ X 1 course, 0% Id reduction; miniBEAM X 1 course, 0% Id reduction</td>
</tr>
<tr>
<td>Interval from last chemotherapy to vaccine</td>
<td>6 wk</td>
</tr>
</tbody>
</table>

* VAD, vincristine (2 mg over 5 days), Adriamycin (9 mg/m²/day for 5 days by slow continuous i.v. infusion), and dexamethasone (40 mg/day orally for 5 days).
+ HDC, high-dose cyclophosphamide (4 g/m² i.v.).
antigen-pulsed DCs derived from adherent PBMCs, and that the response was not ablated by high-dose chemotherapy.

**DISCUSSION**

Whereas the immunogenicity of lymphoma Id protein (12-17) or peptide (18) is established, direct evidence showing the immunogenicity of Id in myeloma patients is lacking. Id-specific T cells could be isolated *de novo* from the peripheral blood of patients with early stage disease (19) and from a healthy bone marrow donor after vaccination with Id in the presence of a carrier (20). These observations suggest the immunogenicity of myeloma Id, at least in patients with early disease or in normal individuals. However, it remained unclear whether myeloma Id was immunogenic in patients with advanced-stage malignancies whose immune systems were generally severely suppressed, due to both previous chemoradiotherapy and progressive deterioration of the immune system associated with the disease itself. Furthermore, even if Id-specific responses could be induced, it remained to be determined whether the responses had any antimyeloma effect. In this study, we therefore set out to investigate if it was possible to induce a beneficial antimyeloma immune response *in vivo* using myeloma Id in a patient with advanced myeloma. DCs were used as carriers for the myeloma
Id to provide the second signal needed for optimal activation of the immune system.

We demonstrated that it was possible to use DCs to induce Id-specific immune responses in a patient with advanced myeloma. Unlike a previous clinical study of DC vaccination (6), the DCs given to this patient were expanded from adherent PBMCs cultured in IL-4 and GM-CSF. The successful generation of immune responses to the vaccine suggests that such expanded cells can function adequately in their ability to uptake, process, and present antigen loaded ex vivo. The resultant immune responses were characterized by MHC-dependent T-cell proliferation and secretion of IFN-γ and B-cell production of anti-Id antibodies. The responses were blocked by both MHC class I and class II antibodies, indicating the presence of T-cell epitopes recognized by both CD4 and CD8 T cells. Whether or not the epitopes are distinct from each other remains to be determined, although our recent results that demonstrated cross-reactivity of T-cell lines generated from Id with those generated from Id CDR3 peptide in a patient with IgA myeloma (21) would suggest that they may both reside within VH CDR3. The dual T-cell responses observed in this patient are not unlike those observed in a previous study involving Id vaccination in a murine model of lymphoma (22) and our previous in vitro study of lymphoma Id VH CDR3 peptide (18). There was also a corresponding fall in the serum Id levels, suggesting a reduction in tumor load in vivo. However, the fall in Id levels was transient and minor, despite further vaccination. The transient response occurred in the face of a progressive increase in the immune responses. The reason for this tumor escape from immune responses is unclear. We speculate that the increased transforming growth factor β secretion associated with active myeloma may play a role by down-regulating the T-cell function. We did not detect any circulating transforming growth factor β (data not shown) in any of the serum samples we tested using an ELISA detection system, but this could be explained by the binding of the cytokine to cell surfaces.

CTL analysis also suggested that Id-primed immune responses could potentially have an antmyeloma effect. Although CTLs for Id-loaded targets were not detected in fresh peripheral blood lymphocytes after vaccination, a T-cell line generated from postimmunized PBMCs was able to lyse Id-pulsed autologous targets repeatedly, albeit at a very low lysis level. Furthermore, Id-primed T cells could recognize and proliferate when exposed to autologous myeloma cells. This finding sug-
gests that the myeloma cells could process and present endog-
neous Id to T cells.

Due to disease progression, high-dose myeloablative
chemotherapy was administered to this patient after three vac-
cinations. This provided us with the opportunity to investigate
the fate of the immune responses after high-dose chemotherapy.
We observed that T cells isolated from fresh peripheral blood
taken after the high-dose chemotherapy retained their ability to
respond to rechallenge in vitro with Id. The T cells showed
proliferation and secreted IFN-γ to Id in a dose-dependent
manner. The persistence of the T-cell response to Id, even after
high-dose chemotherapy, suggests that it may provide a long-
lasting immunity against Id and myeloma cells.

Our results therefore suggest that adherent PBMC-derived
DCs can be used efficiently as a carrier for the presentation of
myeloma Id to elicit potentially beneficial immune responses,
even in a patient with advanced-stage myeloma who had previ-
ously been heavily treated with chemotherapy. The immune
responses thus generated are strong and are not ablated by
high-dose chemotherapy. However, further work is needed to
optimize the vaccination schedule. Such a therapeutic approach
may be useful for patients with minimal residual disease to
reduce the relapse rate of the disease.

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