Vaccination with Dendritic Cell/Tumor Fusions following Autologous Stem Cell Transplant Induces Immunologic and Clinical Responses in Multiple Myeloma Patients

Jacalyn Rosenblatt1, Irit Avivi4, Baldev Vasir2, Lynne Uhl1, Nikhil C. Munshi2, Tami Katz4, Bimalangshu R. Dey3, Poorvi Somaiya1, Heidi Mills1, Federico Campigotto2, Edie Weller2, Robin Joyce1, James D. Levine1, Dimitrios Tzachanis1, Paul Richardson2, Jacob Laubach2, Noopur Raje3, Vassiliki Boussiotis1, Yan Emily Yuan1, Lina Bisharat4, Viki Held4, Jacob Rowe4, Kenneth Anderson2, Donald Kufe2, and David Avigan1

Abstract

Purpose: A multiple myeloma vaccine has been developed whereby patient-derived tumor cells are fused with autologous dendritic cells, creating a hybridoma that stimulates a broad antitumor response. We report on the results of a phase II trial in which patients underwent vaccination following autologous stem cell transplantation (ASCT) to target minimal residual disease.

Experimental Design: Twenty-four patients received serial vaccinations with dendritic cell/myeloma fusion cells following posttransplant hematopoietic recovery. A second cohort of 12 patients received a pretreatment vaccine followed by posttreatment vaccinations. Dendritic cells generated from adherent mononuclear cells cultured with granulocyte macrophage colony-stimulating factor, interleukin-4, and TNF-α were fused with autologous bone marrow–derived myeloma fusion cells using polyethylene glycol. Fusion cells were quantified by determining the percentage of cells that coexpress dendritic cell and myeloma fusion antigens.

Results: The posttransplant period was associated with reduction in general measures of cellular immunity; however, an increase in CD4 and CD8+ myeloma-specific T cells was observed after ASCT that was significantly expanded following posttransplant vaccination. Seventy-eight percent of patients achieved a best response of complete response (CR) + very good partial response (VGPR) and 47% achieved a CR/near CR (nCR). Remarkably, 24% of patients who achieved a partial response following transplant were converted to CR/nCR after vaccination and at more than 3 months posttransplant, consistent with a vaccine-mediated effect on residual disease.

Conclusions: The posttransplant period for patients with multiple myeloma provides a unique platform for cellular immunotherapy in which vaccination with dendritic cell/myeloma fusion fusions resulted in the marked expansion of myeloma-specific T cells and cytotereuction of minimal residual disease.

Introduction

Advances in biologically based therapy with agents such as bortezomib and lenalidomide have resulted in high rates of disease response and improved long-term outcomes for patients with multiple myeloma (1). However, patients uniformly experience progression due to the persistence of resistant disease. The unique efficacy of cellular immunotherapy is supported by the observation that allogeneic hematopoietic stem cell transplantation is curative for a subset of patients due to the graft versus disease effect mediated by allo-reactive lymphocytes (2–7). Conversely, allogeneic transplantation is associated with significant morbidity and mortality secondary to the lack of specificity of the allo-reactive response, which results in graft versus host disease. A major area of investigation is focused on developing strategies to elicit myeloma-specific immune responses that selectively eliminate malignant cells.

We have developed a tumor vaccine in which patient-derived myeloma cells are fused with autologous dendritic cells such that a broad array of tumor antigens are presented in the context of the antigen presenting machinery of the dendritic cell fusion partner (8). Dendritic cell/tumor fusions uniquely stimulate both helper and cytotoxic T-cell responses (9). In animal tumor models including multiple
Response to Dendritic Cell/Multiple Myeloma Fusion Cell Vaccination + ASCT

Translational Relevance

The article details results of a clinical study of patients with multiple myeloma who undergo autologous transplantation in conjunction with vaccination with a patient-specific myeloma vaccine created by the fusion of myeloma cells with autologous dendritic cells. Vaccination in the posttransplant period results in the expansion of myeloma-specific T cells. Most significantly, despite the lack of posttransplant maintenance therapy, 47% and 78% of patients achieved a best response of complete response or >90% regression, respectively. Nearly half of those patients only achieved complete response greater than 100 days posttransplant after the period of vaccination, suggesting a role of posttransplant immunotherapy. These data suggest that vaccination posttransplant may impact posttransplant residual disease, potentially changing the paradigm of myeloma therapy. It sets the platform for studying the role of vaccination in conjunction with maintenance therapy in a randomized trial.

Reagents for vaccine characterization and immunologic assays

Purified mouse antihuman monoclonal antibodies (mAb) against HLA-DR, CD80, CD86, CD40, CD83, CD38, and CD138; phycoerythrin (PE)-conjugated mouse antihuman mAbs against CD4; fluorescein isothiocyanate (FITC)-conjugated anti-CD4 [RPA-T4, immunoglobulin G (IgG)1], CD8 (RPA-T8, IgG1), and FITC-conjugated PE-conjugated matching isotype IgG1, IgG2a, IgG2b controls; and purified mouse monoclonal IgG1 (MOPC-21) isotype control were purchased from BD Pharmingen. Monoclonal antibody DF3 (anti-MUC1 N-ter) has been described previously (17). Antihuman CD4 TC-conjugated, matching isotype control (IgG2a) PE-conjugated antihuman mAbs against IFN-γ (mouse IgG1-B27) and PE-conjugated matching isotype controls (rat IgG1-PE and mouse IgG1-PE) were purchased from Invitrogen. FITC-conjugated goat antimouse (IgG1) was purchased from Chemicon International.

Vaccine generation

Bone marrow mononuclear cells were isolated from 20 to 30 cc of bone marrow aspirate by ficoll density gradient centrifugation and cultured in RPMI 1640 culture media containing 2 mmol/L-glutamine (Lonza), heat-inactivated 10% autologous serum, and 10 ng/mL gentamicin (Baxter). In some cases, myeloma cells were cryopreserved in 10% dimethyl sulfoxide (DMSO)/90% autologous plasma, and later thawed at the time of fusion generation. An aliquot of myeloma cells was cryopreserved for subsequent assessment of myeloma-specific immunity.

Dendritic cells were generated from adherent mononuclear cells isolated from a leukapheresis collection and cultured with 1,000 U/mL granulocyte macrophage colony-stimulating factor (GM-CSF; Berlex Wayne/Montville) and 500 IU/mL interleukin (IL)-4 (Cellgenix, Antioch) for 5 to 7 days and matured in the presence of 25 ng/mL TNF-α (Cellgenix) for 2 to 3 days. Dendritic cell/tumor fusions were generated using polyethylene glycol (PEG) as previously described (14, 18). Dendritic cell/tumor fusions were quantified by determining the percentage of cells that coexpress dendritic cell (CD80, CD86, and CD83) and tumor-associated (CD38 and CD138) antigens by immunohistochemical analysis. The cell product was cryopreserved without further manipulation in autologous plasma (90%) and DMSO (10%) in single dose vial of 5 × 10⁵ to 5 × 10⁶ fusion cells (depending on cell yields). The sterility of the product was confirmed by mycoplasma, endotoxin, and sterility assays. At time of vaccine administration, the fused cells were thawed, assessed for viability and sterility, and irradiated with 30 cGy.

The capacity of the fusion cell preparation to stimulate alloergic T-cell proliferation was assessed by coculturing 1 × 10⁵ T cells obtained from leukopak collections with multiple myeloma cells, dendritic cells, or fusion cells at a ratio of 10:1 for 5 days. T-cell proliferation was determined by measuring incorporation of [³H]thymidine following overnight pulsing (1 μCi/well) of triplicate samples.
Study schema

Patients received up to 1 year of primary induction therapy. Stem cell mobilization was accomplished with cyclophosphamide (2.5 or 3 g/m²) followed by granulocyte colony-stimulating factor. A minimum of \(2 \times 10^6\) CD34+ cells/kg was required to proceed with high-dose chemotherapy (melphalan 200 mg/m²).

Vaccine administration

Patients received three posttransplant vaccinations given at 4-week intervals. Patients in the second cohort received an additional vaccination before stem cell mobilization. GM-CSF (100 \(\mu\)g) was administered as a subcutaneous injection at the vaccine site on the day of vaccination and for 3 days thereafter. Patients were evaluated weekly during the period of vaccination and then monthly for 6 months after the completion of vaccination.

Assessment of myeloma-specific immunity

Peripheral blood mononuclear cells (PBMC) were collected before stem cell mobilization and pretransplant vaccination (cohort 2), before each posttransplant vaccination, and at 1, 3, and 6 months postvaccination. At the completion of the study, \(1 \times 10^6\) cells were cultured for 5 days with autologous myeloma lysate generated by repeated freeze–thaw cycles of \(1 \times 10^5\) autologous myeloma cells. Cells were restimulated with tumor lysate for 6 hours and cultured overnight with 1 \(\mu\)g/mL GolgiStop. Intracellular expression of IFN-γ by CD4+ or CD8+ T cells was determined by fluorescence-activated cell sorting (FACS) analysis. In HLA-A2.1 patients, the number of CD8+ T cells binding the MUC1 tetramer was determined by bidimensional FACS analysis using CD8-FITC and MUC1 tetramer-PE antibody. As measures of general immunity, PBMCs were cocultured with tetanus toxoid (10 \(\mu\)g/mL) for 5 days or the mitogen, phytohemagglutinin (PHA; 2 \(\mu\)g/mL) for 3 days, and the proliferative response was quantified by measuring incorporation of \(^{3}H\)thymidine following overnight pulsing (1 \(\mu\)Ci/well). Levels of regulatory T cells were quantified by determining the percentage of CD4/CD25 high T cells using bidimensional FACS analysis. Expression of FOXP3 by CD4/CD25 cells was measured using intracellular FACS analysis.

Clinical disease assessment

Disease status was evaluated by serum and urine protein electrophoresis, serum light chain quantification, skeletal survey, and bone marrow aspiration, and biopsy. Disease response was assessed according to the international myeloma working group uniform response criteria (19).

Statistical analysis

For analysis of immune response to vaccination, Wilcoxon signed rank test and Wilcoxon rank sum test were used to compare paired and independent samples, respectively. Progression-free survival, defined as the time from the date of transplantation to the date of disease progression or death from any cause, is estimated using the Kaplan–Meier approach. Statistical analysis was conducted using SAS/STAT software, version 9.2 of the SAS System for Windows Copyright 2002 to 2008 (SAS Institute, Inc.).

Results

Patient characteristics

Twenty-four and twelve patients were vaccinated in the first and second cohorts, respectively. Twenty-six patients were enrolled into the first cohort, of which 24 were vaccinated; 19 patients were enrolled into the second cohort, of which 12 were vaccinated. Nine patients were removed from study before receiving vaccination for the following reasons: two patients developed an intercurrent illness during pretransplant therapy and did not undergo an autologous transplant; one patient was found to have...
amyloidosis and was removed from study; two patients chose not to undergo autologous transplantation; one patient did not respond to pretransplant therapy and underwent an allogeneic rather than an autologous transplantation, and two patients withdrew consent and chose to be treated with standard of care autologous transplantation without vaccination. In one instance, vaccination could not be made according to specification and the patient was removed from study.

Patient characteristics are summarized in Table 1. Patients received a median of two regimens before initiating stem cell mobilization with the goal of achieving maximal cytoreduction before transplantation. Therapy consisted of thalidomide-, lenalidomide-, and bortezomib-based regimens in 11 (30.5%), 7 (19%), and 24 (67%) patients, respectively. Eleven patients (30.5%) received lenalidomide, bortezomib, and dexamethasone (RVD) as part of their pretransplant therapy.

Vaccine characteristics
Mean yield of the dendritic cell and multiple myeloma cells was $1.74 \times 10^8$ and $6.5 \times 10^7$ cells, respectively. Mean fusion efficiency as determined by the percentage of cells that coexpressed unique dendritic cell (CD80, CD86, and/or CD83) and multiple myeloma (CD38 and/or CD138) antigens was 38% (Fig. 1). The mean dose administered was $3.6 \times 10^6$ fusion cells. Mean viability of the dendritic cell, myeloma, and fusion preparations was 87%, 87%, and 79%, respectively. The dendritic cell/multiple myeloma fusion preparations exhibited potent antigen-presenting capacity as evidenced by their stimulation of allogeneic T-cell proliferation with a mean stimulation index of 29.9, similar to that observed with the dendritic cell preparation before fusion (mean stimulation index of 49.8). In contrast, the unfused myeloma cells showed minimal capacity for T-cell stimulation (mean stimulation index of 12.7).

Adverse events
Toxicities judged to be possibly related to vaccination are summarized in Table 2. All vaccine-associated toxicities were of grade 1–2 intensity. The most common toxicity was erythema and induration at the vaccine injection site associated with T-cell infiltration on biopsy. The other common side effects were transient pruritis, rash, fatigue, fever, and myalgias. One patient had a transient elevation in the antinuclear antibody (ANA) level without clinical evidence of autoimmunity. One patient developed transient grade 2 leukopenia, but no evidence of graft compromise was observed following vaccination.

Posttransplant immune reconstitution
Consistent with prior reports, the posttransplant period was associated with the relative suppression of general measures of immunity following autologous transplant. PBMC were collected at the indicated time points and incubated with 2 μg/mL of PHA (A) or tetanus toxoid (B) at 10 μg/mL. Proliferation was measured by incorporation of tritiated thymidine. Values are presented as a stimulation index (proliferation of stimulated/unstimulated cells). The results are presented as mean ± SEM from 33 patients.

Table 2. Related adverse events

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<tr>
<td>(erythema, itching)</td>
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Figure 2. Depression of general measures of immunity following autologous transplant. PBMC were collected at the indicated time points and incubated with 2 μg/mL of PHA (A) or tetanus toxoid (B) at 10 μg/mL. Proliferation was measured by incorporation of tritiated thymidine. Values are presented as a stimulation index (proliferation of stimulated/unstimulated cells). The results are presented as mean ± SEM from 33 patients.
measures of cellular immunity. Decreased levels of CD4+ T cells and the inversion of the CD4/CD8 ratio for greater than 6 months posttransplant was seen (data not shown). T-cell proliferation in response to in vitro exposure to the T cell mitogen, PHA, or the recall antigen, tetanus toxoid, was markedly depressed in the early posttransplant period and did not fully recover by 6 months posttransplant (Fig. 2).
Impact of vaccination on myeloma-specific immunity

Vaccination resulted in the marked expansion of myeloma reactive lymphocytes, as determined by percentage of CD4 and CD8^+ T cells expressing IFN-γ in response to ex vivo exposure to autologous tumor lysate (Fig. 3A–D). All evaluable patients showed at least a two-fold expansion of myeloma-specific CD4^+ and/or CD8^+ T cells. The median percentage of myeloma-specific CD8^+ T cells before transplant was 0.64, which reached a peak of 6.0 postvaccination (P < 0.05). The median percentage of myeloma-specific CD4^+ T cells before transplant was 0.43 and increased to 4.0 postvaccination, respectively (P < 0.05). Vaccination resulted in a mean log_{10}-fold increase or 8.32 [95% confidence interval (CI), 4.68–15.14] and 9.55 (95% CI, 5.37–16.98) in CD8 and CD4^+ myeloma-specific T cells, respectively. Vaccination was associated with the expansion of T cells targeting the myeloma-specific antigen, MUC1. In a cohort of patients who were HLA-A2, the median percentage of MUC1-specific T cells was 0.12 pretransplant, and increased to 1.84 at 3 months after completion of vaccination (P < 0.05), representing a median fold increase of 17.5 (Fig. 4). Concomitant with the expansion of tumor reactive lymphocytes, regulatory T cells remained at low levels in the first 6 months posttransplant (Fig. 5).

A rise in tumor reactive T cells was observed following autologous transplantation before vaccination (cohort 1), which was further boosted following vaccination with dendritic cell/multiple myeloma fusions. The mean log_{10}-fold increase in myeloma-specific CD8^+ T cells from pre-mobilization to posttransplant and from premobilization to posttransplant vaccination time points.
to peak postvaccination was 6.76 (95% CI, 3.02–15.49) and 11.48 (95% CI, 4.17–32.36), respectively. Similarly, CD4+ T cells premobilization and at peak postvaccination were 3.55 (95% CI, 1.58–8.13) and 9.55 (95% CI, 5.37–16.98), respectively. Of note, no difference in peak levels of CD4+ or CD8+ circulating myeloma-specific T cells was observed between the cohort receiving a pretransplant vaccine and that undergoing posttransplant vaccination alone (P = 0.185 and 0.689, respectively).

Clinical response
Seventy-eight percent of patients achieved a complete response (CR) or very good partial response [VGPR; 47% CR/near CR (nCR); 31% VGPR]. Thirty-one percent achieved a CR/nCR in the early posttransplant period, whereas an additional 17% (six patients: four from VGPR, two from partial response) achieved CR/nCR as best response only after day 100 posttransplant after undergoing vaccination. The presence of late responses several months after ASCT is consistent with an impact of vaccine therapy on posttransplant residual disease. This response is illustrated by minimal residual disease analysis in a representative patient for whom transplant resulted in the further expansion of myeloma-specific T cells. This provided an ideal platform for vaccination, which resulted in the further expansion of myeloma-specific T cells in the context of low levels of regulatory T cells.

Discussion
We report on the use of a patient-specific myeloma vaccine to elicit antimyeloma immunity and target minimal residual disease posttransplant. The vaccine consists of a hybridoma of patient-derived myeloma cells and autologous dendritic cells with the potential to evoke a polyclonal response directed against multiple antigens, including those unique to a particular patient. In preclinical studies, fusion cells have been shown to more potently stimulate antitumor immunity than single antigen peptide vaccines (20), and have showed the ability to eradicate established metastatic disease (11). Fusion cells are unique in eliciting a broad CD4+ and CD8+-mediated response and in targeting tumor heterogeneity. In a phase I study of dendritic cell/multiple myeloma fusions, vaccination was well tolerated, induced antmyeloma immunity in late stage patients and resulted in prolonged disease stability (14).

ASCT in patients with multiple myeloma results in high rates of disease response and a prolonged period of remission compared to standard chemotherapy, but is not curative (21). The period of posttransplant lymphopoietic reconstitution is associated with enhanced responsiveness to cancer vaccines due to the depletion of inhibitory elements such as regulatory T cells that mediate tumor-associated tolerance. In this study, we showed that vaccination with dendritic cell/multiple myeloma fusions following ASCT was feasible, well tolerated, associated with the induction of antimyeloma immunity and conversion of patients from PR to CR/nCR in the late posttransplant period. An approximately 10-fold expansion of myeloma-specific CD4 and CD8+ T cells was observed as manifested by the percentage of T cells expressing IFN-γ following ex vivo exposure to autologous tumor lysate. We also showed a 15-fold increase in MUC1+ T cells as evidence for the vaccine-mediated expansion of T cells with specificity for myeloma-associated antigens. As predicted in preclinical models, the early posttransplant period was characterized by the suppression of general measures of cellular immunity, but the paradoxical moderate expansion of myeloma reactive T cells in the context of low levels of regulatory T cells. This provided an ideal platform for vaccination, which resulted in the further expansion of myeloma-specific T cells.

To date, myeloma vaccines have focused on the targeting of individual myeloma-associated antigens including idioype, WT1, survivin, hTERT, and NY-ESO (22–24). Although vaccination has resulted in antigen-specific immunity particularly in patients with low-volume disease, clinical efficacy has been uncertain. In this study, 47% of patients achieved a CR as best response and 78% of patients achieved at least a VGPR, comparing favorably to other studies combining bortezomib and/or lenalidomide induction with ASCT (25). Of note, nearly 33% of CRs occurred greater than 100 days posttransplant, after undergoing vaccination. Although delayed effects of chemotherapy may be observed, the significant number of late responses in the absence of maintenance therapy is strongly suggestive of a vaccine-mediated effect.

Although there is strong rationale for the use of patient-specific vaccines that express multiple antigens, there is potential concern for the feasibility of this approach and its applicability across different medical centers. In patients...
with multiple myeloma, there is ready availability of autologous tumor cells via bone marrow aspiration. Vaccine production was successful in 98% of patients and the process of hybridoma generation is feasible for centers with experience in cell manipulation. Another concern is the reestablishment of tumor tolerance over time facilitating disease progression. The negative check point costimulatory molecules embodied in the PD-1/PDL-1 pathway are critical mediators of tumor anergy (26). In an ongoing study, we are evaluating the effect of combining vaccination with dendritic cell/myeloma fusion cells and PD-1 blockade following autologous transplantation.

Patients in this study did not receive maintenance therapy with lenalidomide. Recent randomized studies have showed that lenalidomide maintenance therapy following autologous transplantation results in improved progression-free and overall survival (27, 28). In vitro studies show that lenalidomide augments immune response to vaccines (29), suggesting a potential for synergy between lenalidomide and vaccines in the postautologous transplant setting. Combining vaccination with maintenance lenalidomide following autologous transplantation is an area worthy of study. In summary, this study shows that potent antitumor immune responses and elimination of posttransplant residual disease can be achieved with an autologous tumor vaccine administered in the early posttransplant period. A randomized trial is planned to examine the impact of posttransplant vaccination on disease-free and overall survival.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors' Contributions
Conception and design: J. Rosenblatt, P.G. Richardson, D.E. Avigan
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Rosenblatt, I. Avivi, B. Vasir, I. Uhl, T. Katz, P. Somaiya, R. Joyce, J. Levine, D. Tzachanis, P.G. Richardson, J. Laubach, N.S. Raje, V.A. Boussiotis, Y.E. Yuan, V. Held, D.E. Avigan
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Rosenblatt, I. Avivi, B. Vasir, N.C. Munshi, T. Katz, P. Somaiya, F. Campigotto, E. Weller, P.G. Richardson, L. Bisharat, D.E. Avigan
Writing, review, and/or revision of the manuscript: J. Rosenblatt, I. Avivi, L. Uhl, Nühil C. Munshi, B. Dey, P. Somaiya, F. Campigotto, R. Joyce, P.G. Richardson, N.S. Raje, V.A. Boussiotis, J.M. Rowe, K.C. Anderson, D. Kufe, D.E. Avigan
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Rosenblatt, L. Uhl, N.C. Munshi, P. Somaiya, E. Weller, Y.E. Yuan, L. Bisharat
Study supervision: J. Rosenblatt, D.E. Avigan
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