

Novel Biologically Based Therapies for Multiple Myeloma

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ABSTRACT

Multiple myeloma (MM) remains incurable even with high-dose therapy and stem cell transplantation, and we are developing biologically based therapies to improve outcomes. First, myeloma cells specifically adhere to extracellular matrix (ECM) proteins and bone marrow stromal cells (BMSCs), localizing them in the BM and conferring resistance to apoptosis; agents that block adhesion restore sensitivity to treatment. Second, adherence of MM cells to BMSCs upregulates nuclear factor κ B (NF κ B)-dependent interleukin (IL)-6 transcription and secretion within BMSCs, promoting growth and survival of MM cells. Protease inhibitors not only induce apoptosis of tumor cells, they also inhibit activation of NF κ B and upregulation of IL-6 in BMSCs triggered by tumor cell adhesion. Third, proliferation of MM cells triggered by IL-6 is mediated via the mitogen-activated protein kinase (MAPK) cascade, dexamethasone-induced apoptosis is mediated via activation of related activated focal adhesion kinase (FAK), and the protective effect of IL-6 against dexamethasone-induced MM cell apoptosis is mediated via SH2-containing protein tyrosine phosphatase (SHP2 phosphatase). Delineation of these pathways will help us derive treatment strategies for triggering apoptosis, overcoming dexamethasone resistance, and inhibiting survival signals. Fourth, adhesion of MM cells to BMSCs also upregulates vascular endothelial growth factor (VEGF) secretion; VEGF triggers MAPK activation and proliferation in MM cells, and VEGF receptor inhibitors block MM cell proliferation, suggesting their potential clinical utility. Finally, in addition to antiangiogenic effects, thalidomide and its potent analogs (immunomodulatory drugs [IMiDs]) induce apoptosis or G₁ growth arrest in MM cells resistant to conventional therapy, providing the framework for a new treatment paradigm to target both the MM cell and the microenvironment, overcome classic drug resistance, and achieve improved outcome.

A second translational research program is based on enhancing allogeneic and autologous anti-MM immunity to improve the outcome of high-dose therapy and stem cell transplantation. Basic laboratory studies derive treatment protocols, and conversely, mechanistic evaluation of immune responses observed in patients on clinical trials identifies immune effector cells and novel target antigens. Donor lymphocyte infusions (DLIs) given to treat relapsed MM after allografting can mediate the graft-vs.-myeloma (GVM) effect that manifests as clinical responses; evaluation of these responses has permitted identification of both clonal T cells mediating GVM and their target antigens. The ultimate goal is to generate antigen-specific donor T cells to treat minimal residual disease (MRD) after allografting. Finally, multiple strategies to generate autologous anti-MM immunity form the basis for novel vaccination and adoptive immunotherapy protocols to treat MRD after autografting. These will target either patient-specific (idiotype) or shared (Muc-1 and the catalytic subunit of telomerase) antigens, or whole tumor cells (CD40-activated MM cells or fusions of MM cells with autologous dendritic cells).

INTRODUCTION

Multiple myeloma will newly affect 13,700 individuals in the United States in 2000.¹ Conventional melphalan and prednisone therapy and combination chemotherapy regimens achieve responses, but few complete responses.² High-dose treatment strategies increase response rates, including complete responses, but few if any patients are cured.^{3,4} We have therefore attempted to derive novel biologically based therapies to improve outcome and achieve prolonged disease-free survival and ultimate cure.

METHODS

We have carried out a series of laboratory and derived clinical studies using MM cell lines and freshly isolated patient cells. These studies used previously described techniques to study Ku expression in MM,⁵ antitumor activity of proteasome inhibitors (T. Hideshima, P. Richardson, D. Chauhan, et al., unpublished data) and thalidomide and its analogs,⁶ cell signaling that mediates myeloma cell growth and apoptosis,⁷⁻¹¹ novel approaches for allografting to abrogate graft-vs.-host disease while preserving the GVM effect (E.P. Alyea, E. Weller, R.L. Schlossman, et al., unpublished data),¹² improved methods for purging tumor cells from autografts,¹³ and novel vaccination and adoptive immunotherapy approaches (J.L. Schultze, K.C.A., M.H. Gilleece, et al., unpublished data; N. Raje, T. Hideshima, D. Avigan, et al., unpublished data).¹⁴

RESULTS AND DISCUSSION

Novel Chemotherapeutics

Multiple lines of evidence suggest that the precursor cell in multiple myeloma is a cytoplasmic μ -positive B cell that has undergone antigen selection and somatic hypermutation in the lymph node but has not yet undergone isotype class switching. Chromosomal translocations involving the immunoglobulin (Ig) switch region are common, and multiple partner chromosomes have been described. Given that abnormalities in Ig gene rearrangement, IgH class switching, and DNA damage repair are hallmarks of myeloma, we have undertaken studies of Ku expression and function in human myeloma cells.⁵ Ku is a heterodimer composed of Ku70 and Ku86 subunits that binds with high affinity to altered DNA and is essential for double-stranded DNA break (DSB) repair and normal Ig V(D)J recombination. Our studies to date have identified a 69-kDa variant of Ku86 (Ku86v) in some myeloma cells, which neither binds DNA–protein kinase catalytic subunit (DNA-PKcs) nor activates kinase activity and therefore may account for decreased DNA repair and increased sensitivity to radiation and chemotherapy; conversely, Ku86 in myeloma cells confers resistance to therapy and may represent a therapeutic target.

Myeloma cells home to the BM microenvironment, where excess plasma cells characteristic of this disease accumulate. We have demonstrated mechanisms whereby tumor cells specifically adhere to both ECM proteins and BMSCs, as well as changes in cell adhesion molecule profile correlating with egress of tumor cells into the peripheral blood (PB) in the context of progressive disease and plasma cell leukemia (PCL).¹⁵ Adhesion molecules not only localize tumor cells within the BM microenvironment but also have multiple functional sequelae. Adherence to BMSCs confers resistance to apoptosis,¹⁶ and agents that block adhesion, eg, bisphosphonates, can confer sensitivity to treatment. Furthermore, adherence of tumor cells to BMSCs upregulates NF κ B-dependent IL-6 transcription and secretion within BMSCs¹⁷ and also allows for tumor cell secretion of cytokines, eg, transforming growth factor- β , which further enhances IL-6 transcription and secretion in BMSCs.¹⁸ This is of central importance, because our studies have shown that IL-6 is both a growth and a survival factor for myeloma cells.¹⁹ Proteasome inhibitors are novel drugs that inhibit activation of NF κ B²⁰; they induce apoptosis of myeloma cells that are resistant to conventional therapy, partially block tumor cell adhesion to BMSCs, and inhibit the NF κ B-dependent upregulation of IL-6 in BMSCs and related paracrine growth of adherent tumor cells (T. Hideshima, P. Richardson, D. Chauhan, et al., unpublished data). Therefore, they represent a very attractive class of drugs that directly affect tumor cells but also target tumor cell interaction with BMSCs and the paracrine growth and survival signals provided in the marrow milieu.

We have shown that proliferation of myeloma cells triggered by IL-6 is mediated via the MAPK cascade,⁷ suggesting therapeutic strategies based on blocking this pathway in tumor cells. Apoptosis triggered by gamma irradiation, Fas, and dexamethasone is mediated via distinct signaling cascades. For example, apoptosis induced by dexamethasone (but not gamma irradiation or Fas) is mediated via activation of RAFTK.¹⁰ IL-6 is also a survival factor for human myeloma cells, specifically activating SHP2 phosphatase and thereby blocking the activation of RAFTK and related apoptosis in response to dexamethasone.¹¹ Blocking SHP2 activation with small-molecule SHP2 inhibitors may therefore relieve this protective effect. Further delineation of these pathways will help us derive strategies for triggering apoptosis, overcoming dexamethasone resistance, and inhibiting survival signals, which will provide the framework for related novel treatment approaches.²¹

Our recent studies also suggest that adhesion of myeloma cells to BMSCs upregulates VEGF secretion by BMSCs and myeloma cells. Therefore, in addition to examining the effect of VEGF on BM angiogenesis, we are evaluating whether VEGF is a growth and/or survival factor for myeloma cells. Preliminary studies suggest that VEGF induces MAPK activation and proliferation of some myeloma cells and that VEGF receptor inhibitors block proliferation of tumor cells and may therefore be useful clinically. This increase in VEGF may in part account for increased angiogenesis in human myeloma BM. Based on its antiangiogenic activity, thalidomide was recently used very successfully to treat patients with myeloma, even those refractory to conventional therapy.²² Although thalidomide may be acting in myeloma as an antiangiogenic agent, there are multiple other potential mechanisms of action of thalidomide and/or its *in vivo* metabolites.²³ First, thalidomide may have a direct effect on the myeloma cell and/or BM stromal cell to inhibit growth and survival. For example, free radical-mediated oxidative DNA damage may play a role in the teratogenicity of thalidomide and may also have antitumor effects. Second, adhesion of myeloma cells to BMSCs both triggers secretion of cytokines that augment myeloma cell growth and survival and confers drug resistance; thalidomide modulates adhesive interactions and thereby may alter tumor cell growth, survival, and drug resistance. Third, cytokines secreted into the BM microenvironment by myeloma and/or BMSCs, such as IL-6, IL-1 β , IL-10, and tumor necrosis factor (TNF)- α , may augment myeloma cell growth and survival, and thalidomide may alter their secretion and bioactivity. Fourth, VEGF and basic fibroblast growth factor (bFGF)-2 are secreted by myeloma and/or BMSCs and may play a role in tumor cell growth and survival, as well as BM angiogenesis. Given its known antiangiogenic activity, thalidomide may inhibit activity of VEGF, bFGF-2, and/or angiogenesis in myeloma. Finally, thalidomide may be acting against myeloma via its immunomodulatory effects, such as induction of a T helper 1 (Th1) T-cell response with secretion of interferon (IFN)- γ

and IL-2. Understanding which of these mechanisms mediates antimyeloma activity will be critical both to optimally define its clinical utility and to derive analogs with enhanced potency and fewer side effects.

Already, 2 classes of thalidomide analogs have been reported, including phosphodiesterase 4 inhibitors—which inhibit TNF- α but have little effect on T-cell activation—and others that are not phosphodiesterase inhibitors but do markedly stimulate T-cell proliferation as well as IFN- γ and IL-2 secretion.²⁴ In recent studies, we delineated mechanisms of antitumor activity of thalidomide and its potent analogs (IMiDs).⁶ Importantly, these agents act directly, via inducing apoptosis or G₁ growth arrest, in myeloma cell lines and patient myeloma cells that are resistant to melphalan, doxorubicin, and dexamethasone. Moreover, thalidomide and the IMiDs enhance the antimyeloma activity of dexamethasone, and as for dexamethasone, apoptotic signaling triggered by thalidomide and the IMiDs is associated with activation of RAFTK. Most recent studies suggest that treatment with these drugs alters their adherence to BMSCs and fibronectin and abrogates the upregulation of IL-6 and VEGF induced by tumor cell binding. Finally, these drugs appear to upregulate natural killer (NK) cell-mediated killing of myeloma cells. These studies establish the framework for the development and testing of thalidomide and the IMiDs in a new treatment paradigm to target both the tumor cell and the microenvironment, overcome classical drug resistance, and achieve improved outcome in this presently incurable disease.

Novel Immune-Based Strategies

High response rates can be achieved using high-dose therapy followed by stem cell grafting; however, patients are destined to relapse, and few if any are cured. Major obstacles to cure are the excessive toxicity noted after allografting in myeloma, contaminating tumor cells in autografts, and most importantly, the persistence of minimal residual disease after high-dose therapy followed by either allogeneic or autologous stem cell transplantation. In this context, we are developing improved strategies to treat MRD after high-dose therapy followed by allogeneic or autologous stem cell grafting. Most importantly, we are developing multiple approaches for the generation and enhancement of allogeneic and autologous antimyeloma immunity *in vitro* and in animal models. Based on these studies, we are designing clinical trials that couple our treatments to achieve MRD with these novel immune-based therapies for MRD posttransplant in an attempt to achieve long-term disease-free survival and potential cure of multiple myeloma.

We have carried out high-dose therapy followed by T-cell (CD6)–depleted allografting using histocompatible sibling donors in 61 patients with myeloma whose disease remained sensitive to conventional chemotherapy (E.P. Alyea, E. Weller, R.L. Schlossman, et al., unpublished data). The patients included 39

men and 22 women with a median age of 44 years (range, 32–55 years). Most patients presented with advanced-stage myeloma. The majority of patients achieved either complete (28%) or partial (57%) response; importantly, only 17% of patients developed grade 2 or higher graft-vs.-host disease (GVHD), and the transplant-related mortality was only 5%. Therefore, we have shown that allografting can be done safely in myeloma. Indeed, in our center, the overall and progression-free survival rates of allograft and autograft recipients are equivalent, with approximately 40% of patients surviving at 3 years. However, only 20% of patients are disease-free at ≥ 4 years posttransplant. Excitingly, data from our center and others unequivocally demonstrate that donor lymphocyte infusions mediate a GVM effect that can effectively treat relapsed myeloma after allografting.^{12,25} Unfortunately, GVHD is a frequent cause of morbidity and mortality after DLI. At our Myeloma Center, however, 5 of 7 patients who relapsed after CD6-depleted allografting responded—including 3 complete responses—to CD4⁺ T-cell-enriched DLI, in some cases in the absence of GVHD. This raised the possibility that distinct T-cell clones may be mediating GVM vs. GVHD. Given the high response rates but inevitable relapses observed in the setting of allografting for myeloma, we are now testing in a clinical protocol whether CD4⁺ DLI at 6 months after CD6-depleted allografting may mediate GVM, which will effectively treat MRD and thereby improve outcome. To date, 21 patients have undergone CD6-depleted allografting, 18 of whom developed only grades 0–1 GVHD. Eleven of these 18 patients are >6 months posttransplant and have received CD4⁺ DLI. Eight of the 11 patients who received DLI demonstrated further response (including 4 complete responses), suggesting the potential of DLI to treat MRD. Therefore, our studies already suggest that GVM can be adoptively transferred in this fashion. We are also examining T-cell repertoire, based on V β T cell receptor gene rearrangement, to identify those clonal T cells associated with GVM and their target antigens on tumor cells.^{26,27} Already, we have shown that T cells mediating GVM can target idiotypic antigens, and we are presently identifying other target antigens. The goal of these studies is to characterize, isolate, and expand GVM T-cell clones for antigen-specific adoptive immunotherapy.

Although randomized studies convincingly demonstrate a survival advantage for myeloma patients treated with high-dose therapy and autografting compared with those receiving conventional chemotherapy,³ this treatment is not curative. Two sites of MRD contribute to the failure of autografting: in the autograft and in the patient after myeloablative therapy. At our center, to date, we have carried out high-dose therapy and stem cell autografting in 105 patients who presented with advanced-stage myeloma but whose disease remained sensitive to chemotherapy. As in our allografting experience, the majority of patients responded, including 30% complete and 62% partial responses. However, none of these patients are cured. We have produced monoclonal antibodies in the laboratory that have been

used to deplete tumor cells from myeloma autografts.²⁸ We have also evaluated CD34 selection techniques to select normal hematopoietic progenitor cells within autografts.²⁹ However, any one of these methods depletes only 2–3 logs of tumor cells, and >50% autografts still contain MRD. Based on our laboratory data that myeloma cells express Muc-1 and adenoviral receptors, we have specifically transduced tumor cells within myeloma autografts with the thymidine kinase gene (*tK*) using an adenoviral vector with a tumor-selective (Muc-1) promoter, followed by purging tumor cells *ex vivo* by treatment with ganciclovir.¹³ Pilot studies suggest that >6–7 logs of tumor cells can be purged under conditions that do not adversely affect normal hematopoietic progenitor cells, setting the stage for a clinical trial of adenoviral purging before autotransplantation. We are also attempting to generate and expand antimyeloma-specific autologous T cells *ex vivo* for adoptive immunotherapy of MRD in the patient after autotransplant. It is now possible to clone the gene for the patient's specific idiotypic protein, use computer programs to identify gene sequences encoding for peptides predicted to be presented within the groove of class I human leukocyte antigen (HLA) of a given patient's HLA type, and expand peptide-specific T cells *ex vivo*.³⁰ A similar strategy can be used to expand T cells against peptides within shared antigens that are overexpressed on myeloma cells, such as telomerase catalytic subunit (hTERT),¹⁴ Muc-1,³¹ or CYP1B1.³² Strategies are being tested to enhance the immunogenicity of the whole tumor. Our laboratory studies have also shown that autologous T cells do not proliferate to the patients' own tumor cells as targets in an autologous mixed lymphocyte reaction. However, CD40 activation of myeloma cells upregulates class I and II HLA, costimulatory, GRP94, and other molecules, and CD40-activated myeloma cells trigger a brisk autologous T-cell response (J.L. Schultze, K.C.A., M.H. Gilleece, et al., unpublished data). T cells can therefore be harvested from myeloma patients before autografting, expanded *ex vivo* using CD40-activated autologous myeloma cells as stimuli, and given as adoptive immunotherapy to treat MRD posttransplant.

Finally, we are developing and examining the clinical utility of a variety of myeloma vaccines. First, based on our observation that CD40-activated myeloma cells trigger a brisk autologous T-cell response, we will examine the utility of vaccinations of patients with autologous CD40-activated tumor cells. Second, based on our demonstration of the expression of Muc-1 core protein on freshly isolated myeloma cells,³¹ we will construct and evaluate 2 vaccines: recombinant vaccinia virus containing the Muc-1 gene and autologous dendritic cells (DCs) transduced using adenoviral vectors with Muc-1. Excitingly, we have recently shown that myeloma cells can be fused to DCs and that the use of the myeloma cell–DC fusion as an antigen-presenting cell presents the entire myeloma cell as foreign. In a syngeneic murine myeloma model, vaccinations with myeloma cell–DC fusions, but not with myeloma cells or DCs alone, demonstrate both protective

and therapeutic efficacy. Most importantly, we have shown that patient myeloma cells can be fused to autologous DCs, which are readily isolated from either BM or PB,³³ and that autologous myeloma cell–DC fusions can trigger specific cytolytic autologous T-cell responses in vitro (N. Raje, T. Hideshima, D. Avigan, et al., unpublished data). We will therefore translate these findings to the bedside in clinical trials of myeloma-DC fusion vaccines to assess in vivo myeloma-specific T- and B-cell responses, as well as clinical efficacy. Ultimately, vaccinations will be coupled with adoptive immunotherapy in an attempt to treat MRD after autografting and thereby improve outcome.

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