Small Molecule MYC Inhibitor Conjugated to Integrin-Targeted Nanoparticles Extends Survival in a Mouse Model of Disseminated Multiple Myeloma

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Abstract

Multiple myeloma pathogenesis is driven by the MYC oncoprotein, its dimerization with MAX, and the binding of this heterodimer to E-Boxes in the vicinity of target genes. The systemic utility of potent small molecule inhibitors of MYC-MAX dimerization was limited by poor bioavailability, rapid metabolism, and inadequate target site penetration. We hypothesized that new lipid-based MYC-MAX dimerization inhibitor prodrugs delivered via integrin-targeted nanoparticles (NP) would overcome prior shortcomings of MYC inhibitor approaches and prolong survival in a mouse model of cancer. An Sn 2 lipase-labile produg inhibitor of MYC-MAX dimerization (MI1-PD) was developed which decreased cell proliferation and induced apoptosis in cultured multiple myeloma cell lines alone (P < 0.05) and when incorporated into integrin-targeted lipid-encapsulated NPs (P < 0.05). Binding and efficacy of NPs closely correlated with integrin expression of the target multiple myeloma cells. Using a KaLwRij metastatic multiple myeloma mouse model, VLA-4–targeted NPs (20 nm and 200 nm) incorporating MI1-PD (D) NPs conferred significant survival benefits compared with respective NP controls, targeted (T) no-drug (ND), and untargeted (NT) control NPs (T/D 200: 46 days vs. NT/ND: 28 days, P = 0.05 and T/D 20: 52 days vs. NT/ND: 29 days, P = 0.001). The smaller particles performed better of the two sizes. Neither MI1 nor MI1-PD provided survival benefit when administered systemically as free compounds. These results demonstrate for the first time that a small molecule inhibitor of the MYC transcription factor can be an effective anticancer agent when delivered using a targeted nanotherapy approach.

Introduction

Multiple myeloma is a malignancy derived from a clone of plasma cells, the terminally differentiated B-lymphocytes responsible for antibody production. Multiple myeloma is the second most common hematologic malignancy in the United States and accounts for 1% of cancer deaths. Despite recent advances, the 5-year survival rate in patients with multiple myeloma is less than 40% (1). Although multiple myeloma responds initially well to several classes of chemotherapy, (e.g. proteasome inhibitors, immunomodulatory drugs, and alkylating agents), virtually all patients eventually relapse and die from progressive disease.

The b-HLHZIP transcription factor c-Myc (MYC) has long been known to be a powerful oncogene activated in many types of cancer, and is a central driver of myeloma development (2). The expression of MYC increases with disease stage in multiple myeloma, and MYC upregulation may play a central role in the evolution of Monoclonal Gammapathy of Undertermined Significance (MGLUS) into multiple myeloma (3). MYC activation is likely to be an early event in myeloma pathogenesis with MYC rearrangement present in about 15% of newly diagnosed myeloma (1, 4), which may be an underestimation of the prevalence of MYC translocations (5). Further, a transgenic mouse model of myeloma with targeted activation of MYC in germinal center B cells further supports the role of MYC in multiple myeloma (6).

Transcription factor’s relative position downstream as integrators of multiple signaling cascades makes them an attractive therapeutic target. Strategies for inhibition of MYC function include the antisense strategies (7), RNA interference (8), and interference with MYC-MAX dimerization using small molecules (9). Transformation by MYC is dependent upon dimerization with the bHLHZIP protein MAX, because MYC-MAX heterodimers are required for binding of MYC to E-Boxes in the vicinity of target genes (10) to regulate their expression, and modulate numerous biologic functions (11–13). However, MYC remains a challenging target due to the difficulty of inhibiting protein–protein or protein–DNA interactions with small molecules.
(14–17). After years of effort, several small molecule inhibitors of the MYC-MAX interaction were reported (9, 18–21), but development of these compounds has been slowed due to rapid metabolism, poor bioavailability, or inability of the drug to reach inhibitory concentrations in tumors (21). Yet, inhibitors of MYC function might be an effective and powerful therapeutic strategy if these hurdles could be overcome.

We have reported a nanotherapeutic drug delivery approach, termed ‘contact facilitated drug delivery’ (CFDD; ref. 22), that transfers nanoparticle (NP) lipid surfactant components to the targeted cell membrane through a hemifusion complexation process (23). Moreover, we have advanced this technology through the recent development of phospholipid Sn 2 prodrugs that stabilize and sequester the drug in the hydrophobic aspect of the outer lipid membrane of nanocolloids and prevent premature drug escape or metabolism during circulation to target cells (24, 25). Following transfer of the lipid monolayer components to the target cell membrane, cytosolic lipases enzymatically cleave the Sn 2 ester and liberate the drug into the cytosol (25, 26).

The overarching objective of this project was to characterize and demonstrate an integrin-targeted nanotherapy approach that would improve the efficacy of a potent small molecule inhibitor of MYC-MAX dimerization to increase survival in multiple myeloma. Specific goals were to (i) characterize the relative effectiveness and bioavailability of a candidate Sn 2 lipase-labile MYC-MAX antagonist prodrug (MI1-PD) versus free compound (MI1) in myeloma cells, (ii) demonstrate the efficacy of the MI1-PD incorporated into the integrin-targeted NPs, α,β3, versus VLA-4, in human multiple myeloma cell lines, and (iii) assess the survival efficacy of targeted MI1-PD NPs in a metastatic model of multiple myeloma in mice.

Materials and Methods

Cell lines

Cells were cultured in optimized culture media: H929 and U266 (purchased from the ATCC in 2003 and frozen and stocked cells without passage were thawed in January 2012 for this project that were not tested in our place), LP1, UTMC2 and KMS11 (a generous gift from Dr. P. Leif Bergsagel, Mayo Clinic, Scottsdale, AZ), and 5TGM1 myeloma cells (a generous gift from Dr. G. Mundy, University of Texas, San Antonio, TX). All cells were grown in RPMI 1640 (Cambrex Bio Science Walkersville Inc.) and FCS (HyClone; 10%) and 5% CO2. Cells were incubated for 1 hour with 1 mmol/L MnCl2 before all treatments.

Myc inhibitor (MI1) and prodrug (MI1-PD)

The synthesis involved alterations to the index compound (10058-F4) to introduce a short piperidine amine moiety for functionalization as the Sn 2 prodrug (MI1-PD) was synthesized in three steps. Briefly, 4-ethyl benzoaldehyde underwent aldol condensation reaction with rhodamine in the presence of a catalytic amount of Tween 80 in potassium carbonate solution at ambient temperature. The mixture was neutralized with 5% HCl and the precipitant treated with saturated sodium hydrogen sulfite (NaHSO3), which was recrystallized with aqueous ethanol to produce a bright yellow-colored rhodamine derivative in 72% yield (HRMS calc. 249 Da, found MH+ 250 Da). This compound was reacted with mono-boc (tert-butoxycarbonyl) and formaldehyde. Deprotection of the Boc group in presence of 1:1 HCl in dioxane afforded the Myc-inhibitor-1 (5, HRMS calc. 375, found MH+ 376 Da). Finally, the Myc-inhibitor-1 (MI1) was esterified with 1-palmitoyl-2-azelaoyl PC (fatty acid modified oxidized lipid 16:0-9:0 COOH PC; PzaPC) using a dicyclohexyl carbodiimide (DCC)/4-dimethyl amino pyridine (DMAP)–mediated coupling to produce Myc-rhodamine prodrug (MI1-PD) in 43% yield.

α,β3-Integrin homing ligand

The α,β3-integrin antagonist was a quinalone nonpeptide developed by Bristol-Myers Squibb Medical Imaging (US patent 6,511,648 and related patents), which was initially reported and characterized as the 111In-DOTA conjugate RP748 and cyan 5.5
Immunoblot analysis

Western blots were performed for integrin αv and α4 as described previously (31). Integrin αv (Cell signaling), α4 (Santa Cruz Biotechnology, Inc.), anti-β3-actin (Sigma, St. Louis) were primary antibodies. Blots were incubated with horseradish peroxidase–conjugated secondary antibodies (Amersham Biosciences Corp.) and visualized by enhanced chemiluminescence (Fierce Biotechnology).

Flow cytometry using antibodies and fluorescent nanoparticles

Flow cytometry was performed on the human in H929, U266, and STGM1 mouse multiple myeloma cells as described previously (32). Apoptosis was analyzed using Annexin V. Anti-human integrin αvβ3 antibody, clone LM609 (Milppore Corporation), anti-mouse integrin α4 and β1, (eBiosciences), and rhodamine-labeled NPs were used for flow cytometry (FACScalibur flow cytometer; Becton Dickinson Immunocytometry Systems). Analysis was performed using FLOJO software (Tree Star).

Multiple myeloma cell viability assay

MTT (Sigma-Aldrich) was used for cell viability as previously described (33). A total of 5,000 cells per well were plated in 96-well plates with indicated concentrations of drugs. After 24 hours, 10 μL MTT (Sigma-Aldrich) was added, and HCl/isopropanol was added after 4 hours. Absorbance was measured at 570 and 630 nm using a microtiter plate reader (Bio-Rad Laboratories).

Detection of apoptosis

Apoptosis was analyzed on cells treated with 50 μmol/L of M11 and M11-PD at 24 hours using the Annexin V Apoptosis Detection Kit I (BD Biosciences), according to the manufacturer’s instructions.

Studies in the mouse model for myeloma

A KaWrij mouse model was used as described (32). KaWrij mice were inoculated intravenously with 1 x 10⁶ STGM1 cells and distributed into six groups of 6 to 8 mice, and treated intravenously (a) nontargeted (NT) or targeted (T), (b) drug-bearing (D) or no-drug (ND) PFC or micelle NPs. The following treatment cohorts were studied: (i) ND/NT 200 nm PFC NP; (ii) T/ND 200 nm PFC NP; (iii) T/ND 200 nm micelles; (v) NT/ND 20 mm micelles; (vi) T/ND 20 mm micelles. STGM1 cells were injected via tail vein on day 0. NPs were administered by tail vein injection on days 3, 5, 7, 10, 12, and 14 with 50 μL of M11 (0.145 mg/mL) per mouse. Sera were collected on day 17, diluted 1:2 in PBS, and analyzed by serum protein electrophoresis (SPEP) on a QuickGel Chamber apparatus using precasted QuickGels (Helena Laboratories) according to the manufacturer’s instruction. Densitometric analysis of the SPEP traces was performed using the clinically certified Helena QuickScan 2000 workstation, allowing a precise quantification of the various serum fractions, including the measurements of gamma/albumin ratio.

Statistical analysis

All statistical tests were carried out using GraphPad Prism (GraphPad). Statistical comparisons were performed with ANOVA and unpaired t test for the comparison of in vitro drug treatments and SPEPs. The Mantel–Cox test was used for mouse survival curves. Quantitative data are presented as the mean ± SEM with P < 0.05 considered significant.

Results

Bioactivity of the Sn 2 prodrg (M11-PD) and the parent drug (M11) in vitro

The cytotoxic activities of the base drug M11, and the prodrg M11-PD were evaluated and compared in human (H929...
and U266) and mouse (5TGM1) multiple myeloma cell lines at concentrations ranging from 1.0 nmol/L to 100 μmol/L. MTT cell viability assay showed that MI1-PD decreased cell viability more (P < 0.05) than MI1 on an equimolar basis (Fig. 2A). MI1-PD induced significant apoptosis in the three multiple myeloma cell lines, 92%, 91%, and 91% of control, respectively. MI1 also increased (P < 0.05) the amount of apoptosis in these cells, but the magnitude of response was significantly less, 19%, 31%, and 31%, respectively, than that observed with MI1-PD (P < 0.05; Fig. 2B).

Expression of αvβ3-integrin by multiple myeloma cell lines

Nanotherapeutic delivery of MI1-PD is dependent upon the specific binding of NP to target cells, which then allows the formation of a membrane hemifusion complex to afford prodrug transfer. The suitability of using αvβ3-integrin as a multiple myeloma target was assessed by Western blot analysis evaluating the relative expression of the biomarker across a series of human multiple myeloma cell lines. αv-integrin was abundant in H929 and U266 cells and less so in UTMC2 cells. In contrast, little or no αv-integrin was detected with LP1 or KMS11 multiple myeloma cell lines (Fig. 3A). αβ3-integrin in KMS11 multiple myeloma cell lines (Fig. 3A). αβ3-integrin in KMS11 multiple myeloma cell lines was compared using human multiple myeloma cell lines (Fig. 3B). Nontargeted NP had very low nonspecific adherence to any multiple myeloma cells. However, αβ3-integrated NP had high binding to the H929 (64%) and moderate binding to U266 (26%) multiple myeloma cell lines (Fig. 3B). Binding of the αβ3-targeted NP to the LP1 cell line was negligible and no different than the nontargeted control. In anticipation of using these NPs in a mouse model of multiple myeloma, the 5TGM1 murine cell line was evaluated for αvβ3-integrin expression, and was found to express this integrin present at very low levels (8.1%, data not shown).

Expression of VLA-4 by human multiple myeloma cells

The αv-integrin component of the VLA-4 heterodimer was strongly expressed by all human multiple myeloma cell types except LP1, which was only slightly positive (Fig. 3A). Replication of the nonspecific binding of nontargeted NP to multiple myeloma cells yielded a negative result similar to the previous characterization experiment studying the αβ3-integrin. Rhodamine-labeled VLA-4 targeted NP bound to a large percentage of the human cell lines except LP1. As with αvβ3-integrin, the highest surface expression rates for VLA-4 were noted for the H929 and U266 cells. KMS11 and UTMC2 cells, which had low or negligible αvβ3 NP adherence, bound the VLA-4 NP to a greater degree (Fig. 3B). 5TGM1 expressed high levels of integrin β1 (86.6%), αv (90.8%), and also bound the VLA-4 NP (78.5%; Fig. 3C).

Nanoparticle delivery and response to the MI1-PD in myeloma cell lines

Next, four groups of NP with and without peptidomimetic homing ligands, and with and without MI1-PD prodrug, were compared for integrin targeting and drug delivery effectiveness. The dependence of NP targeting on the delivery and efficacy of MI1-PD, on an equivalent molar dosage basis, was evaluated in H929, U266, and KMS11 human and 5TGM1 mouse myeloma cell lines. As a control, free MI1-PD in DMSO potently decreased cell proliferation in all multiple myeloma cell lines relative to the media or DMSO alone (P < 0.05). Free MI1 had lower potency and was less cytotoxic compared with media only or DMSO only (P > 0.05, Fig. 4). MI1-PD alone was highly cytotoxic. We hypothesized that encapsulating MI1-PD within a ligand-targeted lipid-based nanosystem would enhance MI1 delivery with the prodrug form by preventing premature losses during systemic circulation and by protecting the compound within the hydrophobic membrane from plasma enzymatic degradation and hydrolysis, which have been previous barriers to the success of the cMyc inhibitors. Of note, drug-bearing nontargeted NP had negligible cytotoxicity in multiple myeloma cell lines tested. Likewise, multiple myeloma cells exposed to drug-free NP, whether targeted to VLA-4 or the αvβ3-integrin, had no significant impact on cell viability compared with the media or DMSO controls (P > 0.05, Fig. 4). Cell proliferation of the H929 (Fig. 4A) and U266 cells (Fig. 4B), which highly expressed both the αvβ3- and VLA-4 integrin biomarkers, was reduced (P < 0.05) equivalently by NPs targeted to either receptor. Only the NPs targeted to VLA-4 were effective in decreasing the cell viability in the human KMS11
cells, which appreciably expressed VLA-4 and minimal αvβ3-integrin (Fig. 4C). This cell line illustrates the dependence and specificity of NP targeting for efficacious drug delivery. For mouse 5TGM1 cells, which were strongly positive for VLA-4 expression, VLA-4 NPs incorporating MI1-PD effectively decreased cell viability (P < 0.05). In cells with low αvβ3-integrin expression, αvβ3-targeted MI1-PD NPs had little impact on cell viability (Fig. 4D).

Anti-MYC nanoparticles prolong survival in a mouse model of multiple myeloma

The therapeutic potential of VLA-4–targeted MI1-PD–containing NP was evaluated in a preclinical metastatic model of multiple myeloma. KaLwRij mice were inoculated intravenously with 1 × 10^6 5TGM1 cells, and mice were distributed into six groups of 6 to 8 mice and were treated intravenously with (i) ND/NT 200; (ii) T/ND 200; (iii) T/D 200; (iv) NT/ND 20; (v) T/ND 20; and (vi) T/D 20 (Fig. 5B) on days 3, 5, 7, 10, 12, and 14. MI1 and MI1-PD alone without NPs had no survival benefit for 5TGM1/KaLwRij myeloma mice versus DMSO alone (Supplementary Fig. S4). Disease progression was monitored by survival and serial measurements of serum paraprotein. The tumor burden as measured by serum immunoglobulin was decreased (P < 0.05) in mice treated with targeted MI1-PD NPs as compared with respective NP controls (T/D 200: 46 days vs. 28 days, P < 0.05 and T/D 20: 52 days vs. 29 days, P = 0.001; Fig. 5E and F). These data demonstrate the efficacy of VLA-4–targeted anti-MYC
NPs in a preclinical model of multiple myeloma with the smaller 20 nm micellar NP (T/D 20) being more effective than the 200 nm PFC NP. Of note, these data are the first in vivo results utilizing MI1, MI1-PD alone, or incorporated into lipid-based particles; moreover, they represent the initial in vivo use of the 20 nmol/L micelles for targeted drug delivery.

**Discussion**

Development of clinically useful inhibitors of commonly overexpressed MYC oncoprotein has been a long-sought goal. This project demonstrates the preclinical efficacy of a ligand-directed nanomedicine approach to target a lipase-labile c-MYC-MAX inhibitor, MI1-PD, to protect the drug from systemic degradation and to improve its bioavailability. Delivery of the drug (MI1-PD) via a CFDD transfer mechanism promoted by the binding of the NP through integrin targeting to multiple myeloma cells provided effective drug delivery into the target cells in which cytosolic lipases liberated the active compound into the cytosol to exert its biologic effect.

In vivo studies of the VLA-4–targeted MI1-PD NPs employed the orthotopic STG1M1 mouse model of multiple myeloma, since STG1M1 cells expressed VLA-4 robustly. In *in vitro* results for VLA-4–targeted MI1-PD NPs regardless of size recapitulated the *in vivo* findings. VLA-targeted MI1-PD NP conferred significant survival benefit in mice versus control NPs, with 20 nm NPs having a higher survival benefit than the 200 nm NPs (*P* < 0.05). The number of mice surviving in the 20 nm cohort was higher than the 200 nm in any given week, which was further corroborated by the quantification of the gamma peak in the two cohorts. Neither MI1 nor MI1-PD provided survival benefit when administered systemically as free compounds. These results support the contention that the VLA-4–targeted NPs concentrate drug in the tumor and within the cells by overcoming prior issues of rapid systemic degradation and ultimately inadequate multiple myeloma intracellular bioavailability.

*In vitro*, MI1-PD in DMSO was more effective in multiple myeloma cells than equimolar dosages of the free drug analogue, MI1. This improved potency likely reflected improved cellular bioavailability of the phospholipid prodrug. In addition, the distribution of MI1-PD throughout the inner cell membranes may create a drug depot from which the active compound could be liberated over a longer timeframe. Across the range of drug exposure concentrations tested, both compounds decreased cell viability in a parallel monotonic fashion with no evidence of plateau effect noted, indicating that neither intracellular drug release nor transcription factor pathway inhibition were limiting mechanisms. Interestingly, U266 cells, which have low c-MYC expression (3), were sensitive to MI1-PD and MI1, at higher molar exposures, corroborating reports that 10058-F4 can inhibit n-MYC (34, 35).

Integrins VLA-4 and αvβ3-integrins are critical for adhesion of multiple myeloma cells to bone marrow stromal cells, and both integrins have been suggested as therapeutic targets for multiple myeloma treatment (36). Based on the pattern of expression of activated αvβ3 and VLA-4 integrins in multiple myeloma cell lines (Fig. 3), either integrin might be used as a preferential biomarker of human multiple myeloma, but VLA-4 was expressed more widely in the human cell lines. Of the human myeloma cells...
evaluated, all but one expressed VLA-4. One myeloma cell line, LP1, expressed neither α3β1-integrin nor VLA-4 at significant levels, and it did not show any cytotoxic response when treated with either of the two integrin-targeted MI1-PD NPs. The murine 5TGM1 cells expressed high levels of VLA-4 and poorly expressed the α3β1 integrin, and appropriately, VLA-4–targeted MI1-PD NPs were significantly more effective than those targeted to α3 in vitro (Fig. 3). Indeed, others have targeted this integrin with liposomal doxorubicin in preclinical mouse models (37).

While the cellular uptake of free MI1 or MI1-PD was dependent on the concentration of drug exposure in the cell medium, for the targeted NPs, the efficacy of MI1-PD delivered to the myeloma cells was dictated by the target integrin expression level. The nontargeted MI1-PD NPs elicited no significant effects. Two of the human myeloma cell lines, H929 and U266, expressed both biosignatures abundantly and showed effective cytotoxicity when treated with either integrin-targeted MI1-PD NP. Presumably, high expression of the integrin on the target cells accommodated larger number of integrin-targeted NPs, thereby affording higher intracellular drug levels. Given the heterogeneity of VLA-4 and α3β1-integrin expression and likely other biomarkers, a personalized medicine approach founded on prescreening results of myeloma cell biomarker expressions may enhance clinical management. For human myelomas with negligible expression of VLA-4 and α3β1-integrin, as noted for the LP1 cells, further investigation of myeloma cell surface markers will be required to identify alternative targets with adequate expression levels.

In summary, we have developed a nanomedicine therapeutic approach to multiple myeloma using a lipase-labile MYC-MAX inhibitor prodrug carried by integrin-targeted NPs and for the first time showed reduced tumor burden in live mice. The Sn 2 phospholipid prodrug incorporates an analogue of known MYC-MAX dimerization inhibitor. The intracellular lipase-labile prodrug, MI1-PD, had significantly increased potency against myeloma cells in culture compared with its free drug counterpart, most likely due to increased cell bioavailability. When incorporated into lipid surfactant-coated NPs and targeted to VLA-4 or the α3β1 integrin, the MI1-PD was effective against cell lines expressing the biomarker strongly, and less potent when receptor expression was low or absent. In a mouse model of disseminated myeloma, administration of VLA-4–targeted MI1-PD NP conferred significant survival benefit versus nontargeted and drug-free controls. Neither MI1 nor...
ML1-PD provided survival benefit when administered systemically as free compounds. These data provide a strong foundation to reconsider transcription factor antagonism as a viable therapeutic strategy and in particular further pursue anti-MYC nanomedicine approaches to myeloma and perhaps other cancers.

Disclosure of Potential Conflicts of Interest
Washington University (D. Pan and G.M. Lanza) has intellectual property rights to nanoparticle and produg technologies described. The University of Pittsburgh (E.V. Prochownik) has IP rights related to the index compound. No other potential conflicts of interest were disclosed by the other authors.

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