

Novel Biologically Based Therapies for Multiple Myeloma

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Despite improvements in complete responses and prolongation of overall and event-free survival with high-dose therapy, multiple myeloma (MM) remains an incurable disease in the majority of patients [1]. Thus, in order to overcome resistance to standard dose and high-dose therapies and to improve patient outcome, approaches specifically targeting the mechanisms whereby MM cells grow and survive in the bone marrow (BM) are needed. We are attempting to derive novel biologically based therapies focused upon targeting the MM cell as well as its BM microenvironment [2].

Improved understanding of myeloma cell survival in its microenvironment has provided such new targets. Myeloma cells adhere to the extracellular matrix and to bone marrow stromal cells (BMSC), allowing myeloma cells to proliferate, survive and have anti apoptotic effects against conventional chemotherapies. These effects are partially mediated through various cytokine release, including IL-6, VEGF, TNF- α , and IGF-1. The molecular signals mediating these effects include the Ras/Raf MAPK cascade for proliferation and the PI3-K/Akt pathway which provides drug resistance signals. This understanding has now allowed us to evaluate novel therapies that not only directly target myeloma cells but also act on the bone marrow microenvironment, specifically, the molecular and cytokine targets, to overcome drug resistance.

In the past three years, we have used the *in vitro* and *in vivo* animal model systems to define novel therapeutic agents directed at targets specific to both the MM cell and its microenvironment, and have then translated these studies from bench to bedside in the related clinical trials. Thalidomide and its analogous immunomodulatory agents (IMiDs), proteasome inhibitor PS341,

and Arsenic trioxide (As₂O₃), are three such agents which have already demonstrated marked clinical anti-MM activity even in patients with refractory relapsed MM thus confirming the utility of our preclinical models to identify and validate novel therapeutics.

The known anti-angiogenic activity of Thalidomide coupled with the reports of increased angiogenesis in MM BM, provided the rationale for its use in myeloma. Studies during the last 4 years have confirmed efficacy of thalidomide, including refractory relapsed MM [3]. Our more recent studies confirm that Thalidomide and its more potent analogous IMiD, not only act to inhibit angiogenesis, but also act directly on MM cells; change expression of adhesion molecules and abrogate the adhesion of MM cells to BMSCs and block the increased secretion of MM growth and survival factors such as IL-6, TNF- α , VEGF and FGF triggered by binding of MM cells to BMSCs; and additional immune responses by expansion of NK cell number and function against human MM cells [4,5]. Efficacy of IMiD was then demonstrated in a SCID model. A derived clinical Phase I trial of the IMiD CC-5013 has demonstrated stable disease or better results in 20 of 24 (79%) patients. Remarkably, 7 of 11 patients with MM refractory to high dose therapy and Thalidomide achieved either stable disease or responded to escalating doses (5 to 25 mg) of CC-5013, and all 13 patients treated with 50 mg have either stabilized or responded to CC-5013 [6]. This encouraging preliminary clinical data validates the potential of our preclinical models for the development of therapies targeting both the MM cell and its microenvironment and has led to the development of studies with this agent at earlier stage of the disease.

The second class of agents studied is the proteasome

inhibitors. Our prior studies have demonstrated that MM cell adhesion to BMSCs triggers the transcription and secretion of IL-6 in BMSCs via an NF- κ B dependent mechanism. PS-341 blocks NF- κ B activation and mediates anti-MM activity by inhibiting paracrine IL-6 production in BMSCs [7]. Our studies demonstrate that PS341 acts directly on MM cells to induce apoptosis of MM cells resistant to known conventional therapies, overcomes the protective effects of IL-6, and adds to the anti-MM effects of Dexamethasone. Importantly, it acts in the microenvironment to inhibit the binding of MM cells to BMSCs, the transcription and secretion of IL-6 triggered by MM to BMSC adhesion, and BM angiogenesis [8]. Based on exciting animal model results [9] and a confirmed safety profile in phase I study which in fact showed responses in 2 of 2 myeloma patients, a multicenter phase II trial of PS341 in MM was completed last year [10]. Two hundred patients with refractory relapsed MM have been entered in this study; of 54 evaluable patients, 85% achieved response (50% or stable disease (35%).

Arsenic trioxide is another agent we studied that targets both the MM cell and its microenvironment. As₂O₃ at clinically achievable levels induces apoptosis of drug resistant MM cell lines and patient cells via caspase 9 activation. We have observed the additive effects of As₂O₃ with Dexamethasone, observing the ability to overcome the anti-apoptotic effects of IL-6. As₂O₃ also decreases MM cell binding to BMSCs and inhibits IL-6 and VEGF secretion induced by MM-BMSC adhesion [11]. A phase I clinical study has shown response in 3 of 14 relapsed refractory patients; thus prompting the next generation of study that includes dexamethasone and ascorbic acid [12].

Finally, these cellular and signaling studies provide the preclinical rationale for combining these novel agents amongst themselves or with other conventional therapies to enhance efficacy. Ongoing studies will define their utility as primary therapies at earlier stages of the disease. These novel therapies represent a new treatment paradigm targeting both tumor cells and their microenvironment to achieve greater tumor cyoreduction resulting in a possible cure.

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