

# Combination Therapy for Multiple Myeloma: How Far Have We Come?

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Multiple myeloma (MM) is a malignant neoplasm of plasma cells that constitutes 1% of all cancers and 10% of hematologic neoplasms. MM is the second most common hematologic malignancy after non-Hodgkin's lymphoma. It is estimated that 21,700 new cases of MM (approximately 12,190 men and 9,510 women) will be diagnosed during 2012 in the United States, and approximately 10,710 individuals (6,020 men and 4,690 women) will die of the disease [1]. The five-year survival rate for patients with MM is 40%, with younger patients showing higher survival rates than the elderly. However, MM still remains incurable and emergence of drug-resistance is considered to be one of the major causes of relapsed or refractory disease. Research in the last decade has shed new light on the biology of MM and the importance of the bone marrow microenvironment in supporting MM cell growth, survival, and therapy resistance. In addition, significant insight has been gained into the role of natural killer (NK) cells in myeloma progression and the existence of MM cancer stem cells (CSCs) has been established. Hence, with increased understanding of the MM disease and a novel armamentarium of molecularly targeted therapeutic agents, are we close to overcoming the challenge of relapse in MM?

Traditionally, chemotherapy of MM has included corticosteroids (i.e. dexamethasone and prednisone) and cytotoxic drugs (i.e. melphalan, vincristine, cyclophosphamide, and doxorubicin). The mainstay high-dose standard treatment protocol for MM patients is comprised of induction therapy with vincristine, doxorubicin, and dexamethasone (VAD) followed with autologous stem cell transplantation. In recent years, the response rates and survival of MM patients have substantially improved with the introduction of novel agents such as lenalidomide, and bortezomib [2]. Based upon the biochemical rationale that relative to normal cells cancer cells intrinsically experience oxidative stress, researchers have combined oxidative stressors (certain chemotherapeutic drugs and radiation therapy) with agents that deplete intracellular antioxidants, inhibit antioxidant enzyme activity, and/or disrupt mitochondrial membrane potential [3]. To selectively eliminate myeloma cells by oxidative catastrophe, few cytotoxic drugs hypothesized to act via reactive oxygen species-induced oxidative stress (i.e. arsenic trioxide, dexamethasone, bortezomib) have been combined with agents that deplete intracellular antioxidants (i.e. buthionine sulfoximide, ascorbic acid), inhibit antioxidant enzyme activity (i.e. 2-methoxyestradiol), inhibit the secretion of pro-proliferative cytokines (i.e. IL-6 by dexamethasone), and/or other cytotoxic drugs that disrupt mitochondrial membrane potential to release cytochrome c (i.e. bortezomib and farnesyl transferase inhibitors) [4].

Radiation therapy is a powerful treatment modality for MM, yet the use of radiotherapy in MM has been mainly limited to palliative care or myeloablative pre-conditioning regimens [5]. Recently, studies utilizing targeted radiotherapeutic methods such as radioimmunotherapy [5,6], radiovirotherapy [7,8], and bone-seeking radiopharmaceuticals [9,10] have extended the use of ionizing radiation for therapy of systemic MM. Furthermore, combining targeted radiotherapy with radiation-sensitizing chemotherapeutic drugs such as bortezomib [11-13] and dexamethasone [14] can provide additional benefit by improving the overall treatment efficacy in MM.

The bone marrow microenvironment plays an active role in supporting tumor growth, angiogenesis, bone disease, and drug resistance

in MM [15]. Of the various secreted cytokines, paracrine and autocrine regulation by interleukin (IL)-6 plays a particularly important role in emergence of chemoresistance and radioresistance in MM. In a recent study, we reported a correlation between nuclear factor- $\kappa$ B-dependent manganese superoxide dismutase expression and IL-6-induced myeloma cell resistance to dexamethasone and radiation [16]. Thus, one may perceive that novel preclinical studies involving the inhibition of antioxidant pathways may have the potential to enhance myeloma cell responses to radiotherapy and/or chemotherapy.

MM progression has been associated with immune dysregulation, thus novel therapeutic strategies that would augment NK cell function are being tested in MM [17]. In many tumors types, such as hepatocellular carcinoma, breast cancer, and medulloblastoma, a sub-population of self-renewing cells known as cancer stem cells (CSCs) has been established. Since CSCs are particularly resistant to radiotherapy and chemotherapy, novel strategies that target both CSCs and bulk tumor populations can potentially provide improved cure rates of cancer [18]. Recent progress suggests a CD138<sup>+</sup>/CD19<sup>+</sup>/CD20<sup>+</sup>/CD27<sup>+</sup> phenotype for myeloma CSCs. Myeloma CSCs have been shown to be resistant to dexamethasone, cyclophosphamide, and bortezomib but lenalidomide has been shown to target and kill a sub-population of myeloma CSCs. Therapeutic strategies that can target and eliminate CSCs in addition to differentiated myeloma cells have the potential to alleviate therapy resistance challenge faced by the current clinical treatments in MM.

In summary, with increased understanding of MM disease progression and the emergence of therapy resistance, we are ready to design and test novel preclinical and clinical combination therapy protocols involving molecularly targeted chemotherapeutic drugs and oxidative stress inducing agents that may offer improved response rates for MM patients.

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