652. MYELOMA - PATHOPHYSIOLOGY AND PRE-CLINICAL STUDIES, EXCLUDING THERAPY: POSTER III | NOVEMBER 16, 2012

The Anti-Kappa Monoclonal Antibody MDX-1097 Synergizes with Immunomodulatory Drugs to Enhance Antibody-Dependent Cell Cytotoxicity of Multiple Myeloma Cells

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Abstract

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Multiple Myeloma (MM) is a cancer caused by the proliferation of malignant clonal plasma cells in the bone marrow and accounts for 10% of all hematologic malignancies. Recent advances have been made in the treatment and management of MM, however, despite these advances the majority of patients will ultimately relapse and die from their disease within 3–5 years from diagnosis. Several novel therapeutic approaches, including the use of antibody-based therapies, are being investigated to further improve the treatment of MM.

MDX-1097 is a chimeric monoclonal antibody being assessed as a single agent in a Phase 2 clinical trial for the treatment of kappa light-chain restricted (κ-type) MM. MDX-1097 binds to the kappa myeloma antigen (KMA), a tumor-specific membrane-associated protein expressed on malignant plasma cells from patients with K-type MM. Previously we have demonstrated that MDX-1097 exerts its anti-tumour effects through multiple mechanisms, including antibody-dependent cell cytotoxicity (ADCC) in the presence of either normal human peripheral blood mononuclear cells (PBMCs) or purified natural killer (NK cells).

The immunomodulatory drugs (IMiDs) lenalidomide (Revlimid) and pomalidomide (Actimid) are currently in use or being assessed for the treatment of MM. These IMiDs have been shown to exert their anti-tumor effects both directly, via apoptotic mechanisms, and indirectly via a number of different mechanisms including the augmentation of NK-dependent cellular cytotoxicity.

In this study we report that IMiDs and MDX-1097 co-operate to promote enhanced ADCC of MM cells. *In vitr*o treatment of normal PBMCs with IMiDs led to a 1.4-fold higher level of ADCC-mediated cell death of MDX-1097 spiked JJN3 cells (a κ-type MM cell line) compared with vehicle-treated PBMCs from the same donor. Similarly, *in vivo* lenalidomide exposed PBMCs isolated from a MM patient were, on average, 1.8-fold more effective in killing MDX-1097 spiked JJN3 cells *in vitro* compared to PBMC obtained from the same patient prior to lenalidomide treatment. Treatment of JJN3 cells with IMiDs resulted in significantly increased cell surface expression of KMA (lenalidomide: 1.9-fold, $p < 0.001$; pomalidomide: 2.3-fold, $p < 0.01$). These IMiD-treated JJN3 cells, when spiked with MDX-1097 were 1.7-fold more susceptible to ADCC-mediated cell death in the presence of untreated PBMCs, compared to JJN3 cells treated with vehicle alone. This difference in sensitivity to ADCC mediated cell death is presumably due to increased KMA expression resulting in more binding sites for MDX-1097, therefore facilitating recruitment of PB immune effector cells. Furthermore, combining IMiD-treated PBMCs with IMiD-treated, MDX-1097 spiked JJN3 cells resulted in a further increment in ADCC-mediated JJN3 cell death.

This study demonstrates that *in vivo* and *in vitro* treatment of PBMCs with IMiDs engages the PB immune effector cells, leading to increased ADCC-induced κ-type MM cell death in vitro in the presence of MDX-1097. IMiDs also increase cell surface expression of KMA, leading to increased MDX-1097 binding and in turn also enhancing ADCC-induced MM cell killing. Our data provides a rationale for the clinical evaluation of a combination therapy involving both IMiDs and MDX-1097 for the treatment of k-type MM.

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