Clinical Cancer Research

CD38-Targeted Immunochemotherapy in Refractory Multiple Myeloma: A New Horizon

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CD38 is a type II transmembrane glycoprotein that is highly expressed in multiple myeloma and is a promising target for immunotherapy. Daratumumab is a human monoclonal antibody that has potent anti-multiple myeloma activity both as monotherapy and in combination with other multiple myeloma treatments, and has breakthrough designation on this basis. *Clin Cancer Res; 21(12); 2660–2. ©2015 AACR.*

See related article by Nijhof et al., p. 2802

In this issue of *Clinical Cancer Research*, Nijhof and colleagues (1) demonstrate the *in vitro* as well as *in vivo* susceptibility of myeloma cells derived from patients with lenalidomide- and bortezomib-refractory multiple myeloma to daratumumab. The authors suggest that this novel CD38 antibody may offer a new therapeutic approach for multidrug-refractory multiple myeloma. Importantly, they demonstrate that lenalidomide, although no longer active as a therapeutic agent in these patients, can still augment the anti-multiple myeloma effects of daratumumab through the activation of natural killer cells in their model systems. They therefore conclude that patients refractory to multiple drugs may potentially benefit from therapy with daratumumab combined with lenalidomide, as well as in combination with bortezomib (1).

Ideal targeted antigens for cancer immunotherapies include those molecules that demonstrate substantial overexpression on malignant cells (versus normal cells), and are involved in key cellular growth or signaling mechanisms, with these characteristics clearly demonstrated by CD38 in multiple myeloma (2–6). CD38 is a type II transmembrane glycoprotein that functions through receptor-mediated adhesion signaling, as well as through ectoenzymatic activities involved in intracellular calcium mobilization (3–6). Importantly, CD38 shows low expression levels on normal hematopoietic cells and in non-hematopoietic tissues (6, 7). In contrast, high and uniform expression of CD38 has been demonstrated in multiple myeloma (2, 5, 6); this, in combination with its role in cell signaling, makes CD38 an attractive target for antibody therapy in multiple myeloma (Fig. 1).

Despite remarkable progress in the treatment of multiple myeloma over the course of the last decade, the disease remains incurable and typically follows a relapsing, and ultimately refractory, course, with patients requiring multiple lines of therapy (8, 9). Treatment options for multiple myeloma have expanded dramatically over the past decade to include the first-in-class proteasome inhibitor bortezomib, then carfilzomib, and the immunomodulatory drugs thalidomide, lenalidomide, and pomalidomide, with the very recent approval of the histone deacetylase inhibitor panobinostat.

Multiple myeloma harbors various genetic abnormalities by which the disease may be classified into multiple different subgroups (10); however, although this genetic diversity results in a highly heterogeneous disease, characteristic features include enhanced expression of adhesion molecules, increased sensitivity to growth stimuli, upregulation of cell-surface receptor-mediated signaling, resulting in increased tumor growth, survival, resistance, and migration, as well as induction of angiogenesis (11). These processes are driven through complex stimulatory interactions with activated endothelial cells, bone marrow stromal cells, and other cellular components of the bone marrow microenvironment, which result in cytokine and growth factor secretion and the subsequent induction of antiapoptotic signaling (11).

Set against this, daratumumab appears to offer substantial promise for the treatment of multiple myeloma based on extensive preclinical findings and preliminary clinical data. It has a novel mechanism of action that results in enhanced activity in combination with existing standards of care, including first-generation novel agents, such as lenalidomide and bortezomib, as well as other therapeutics (Fig. 1). Specifically, it has also shown a strong signal in preclinical modeling with broad-spectrum killing activity through complement-mediated cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and ADC phagocytosis (ADPC; Fig. 1). The novel target of daratumumab, namely CD38, thus appears to represent a critical pathway in multiple myeloma, and this in turn may result in this monoclonal antibody being less vulnerable to resistance mechanisms, not least due to the broad expression of this target in multiple myeloma cells as well as in the tumor-related microenvironment. This therefore translates into potent anti-multiple myeloma activity regardless of clonal heterogeneity, seen both between and within patients, and so may make this especially attractive as an agent for use broadly in treatment, as well as in specific high-risk subgroups of patients with molecularly driven adverse characteristics (12).

Daratumumab was first evaluated clinically in a phase I trial involving patients with relapsed/refractory multiple myeloma (13). The study employed a standard 3+3 dose escalation with

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doi: 10.1158/1078-0432.CCR-14-3190

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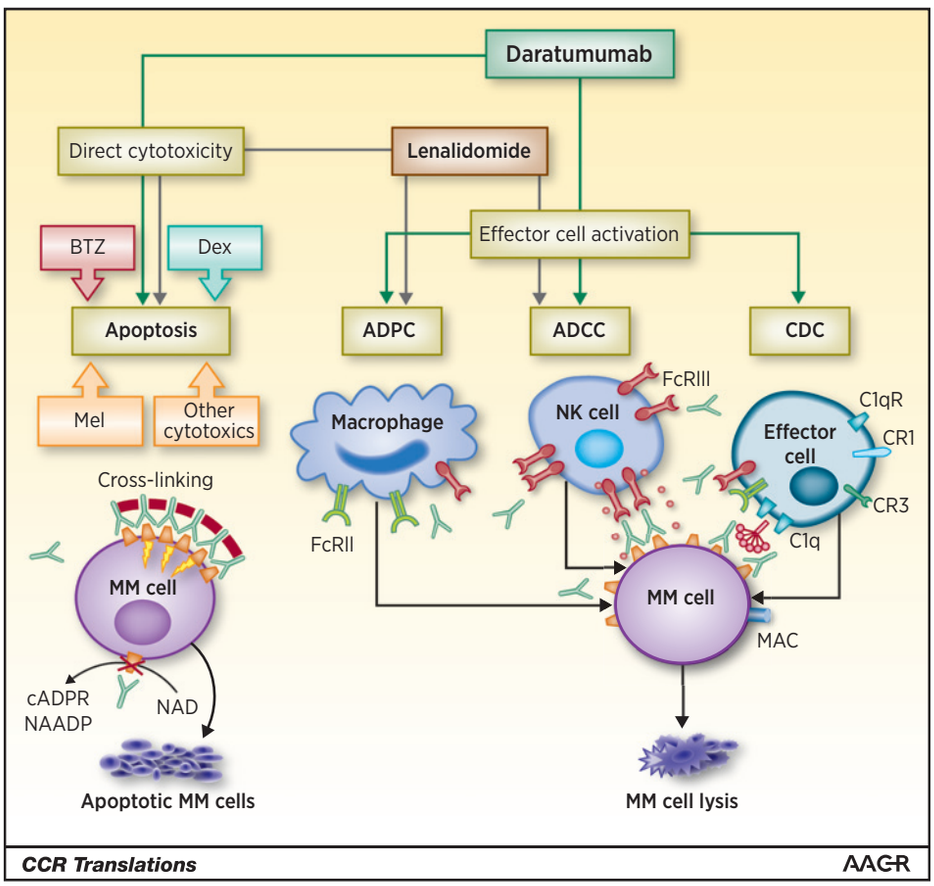

Figure 1.
Mechanisms of daratumumab's anti-myeloma activity. Daratumumab directly targets the myeloma cell through apoptosis induced by cross-linking of daratumumab with FcRs expressed on effector cells and by inhibition of CD38 ADPR-ribosyl cyclase activity. ADPC and ADCC are mediated by natural killer (NK) cells and macrophages through binding of tumor cell–bound daratumumab to FcRs. CDC occurs through interaction between antibody Fc and the complement-activating protein C1q, which in turn leads to opsonization of antibody and activation of complement, resulting in tumor cell phagocytosis. Activation of the membrane attack complex (MAC) through binding of C3b to C3 convertase, which results in the formation of C5 convertase. These mechanisms of daratumumab's anti-myeloma activity are markedly augmented by lenalidomide, as well as by bortezomib (BTZ), melphalan (Mel), and dexamethasone (Dex). ADPR, ADP ribose; FcR, Fc receptor; MM, multiple myeloma. Adapted from Laubach et al. (12).

doses ranging from 0.005 to 24 mg/kg. The median number of prior therapies was 5.5, and 75% of patients were refractory to both lenalidomide and bortezomib. The rate of minimal response or better was 30%, and notably the rate of minimal response or better among patients who received at least 4 mg/kg was 67%, with a partial response (PR) rate of 42%. Treatment-related adverse events included anemia, thrombocytopenia, and infusion reactions. These promising results led to designation of daratumamb by the FDA as a "breakthrough therapy," reflecting the agent's potential to address an important area of unmet medical need.

Daratumumab was partnered with lenalidomide and dexamethasone in a phase I/II trial in which patients with relapsed/refractory disease received lenalidomide 25 mg for days 1 to 21 of a 28-day cycle, dexamethasone 40 mg weekly, and daratumumab 2 to 16 mg/kg weekly for 8 weeks, every other week for 16 weeks, and monthly thereafter (14). This study was informed by the promising preclinical signal seen for this combination as described above (Fig. 1).

In a preliminary analysis involving 20 patients, the rate of PR or better was 75%, with 3 patients achieving CR and 6 patients a very good partial response (VGPR). There were no dose-limiting toxicities, and the most frequent adverse events included neutropenia, thrombocytopenia, and diarrhea, which generally proved manageable with dose reduction and supportive care (14).

A phase II study of daratumumab in the "double-refractory" multiple myeloma patients resistant to both immunomodulatory and proteasome inhibitor therapy has completed enrollment. Results of this study, involving a patient population known to have particularly poor prognosis, are awaited with great interest.

The clinical development of daratumumab has quickly moved forward into phase III clinical trials, including studies evaluating lenalidomide–dexamethasone ± daratumumab and and bortezomib–dexamethasone with ± daratumumab. A study of daratumumab in smoldering multiple myeloma is also under way.

Daratumumab may offer particular utility in these high-risk populations due to its unique mechanism of action. Of note, the safety profile of daratumumab appears to be favorable, with few off-target effects apparent to date, despite concerns regarding potential bystander toxicity associated with its mechanism of action. Ongoing and future investigation will, hopefully, determine the therapeutic index of daratumumab more comprehensively in combination with other agents. Similarly, ongoing studies will also determine the tolerability of daratumumab as a long-term treatment for multiple myeloma, an aspect of considerable importance in specific areas of the treatment algorithm, such as maintenance (12).

In summary, monoclonal antibodies represent a very promising new field of investigation in multiple myeloma, and have dramatically expanded therapeutic horizons to date with great potential apparent as a new therapeutic modality. Daratumumab, in particular, appears to offer strong single-agent activity as well as remarkable efficacy in combination. This agent thus provides a potential breakthrough as a biologically rational approach in the

treatment of multiple myeloma to meaningfully improve patient outcome.

Disclosure of Potential Conflicts of Interest

J.P. Laubach reports receiving commercial research grants from Celgene, Millennium Pharmaceuticals, Novartis, and Onyx Pharmaceuticals. P.G. Richardson is a consultant/advisory board member for Genmab and Janssen. No other potential conflicts of interest were disclosed.

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): P.G. Richardson

Acknowledgments

The authors gratefully acknowledge the editorial support of Michelle Maglio and Megan Hiserodt in the preparation of this article.

Grant Support

J.P. Laubach and P.G. Richardson are supported by the R.J. Corman Multiple Myeloma Research Fund.

Received March 16, 2015; accepted March 19, 2015; published OnlineFirst April 15, 2015.

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