Monoclonal Antibodies in the Treatment of Multiple Myeloma

CHARISE GLEASON,[1] MSN, NP-BC, AOCNP®, HOLLIE DEVINE,[2] MSN, ANP-BC, BETH FAIMAN,[3] PhD, MSN, APRN-BC, AOCN®, DEBORAH DOSS,[4] RN, OCN®, and SANDRA KURTIN,[5] RN, MSN, AOCN®, ANP-C, on behalf of the International Myeloma Foundation Nurse Leadership Board

From [1]Winship Cancer Institute of Emory University, Atlanta, Georgia; [2]The Ohio State University Medical Center, Columbus, Ohio; [3]Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio; [4]Dana-Farber Cancer Institute, Boston, Massachusetts; [5]The University of Arizona Cancer Center, Tuscon, Arizona.

Authors' disclosures of potential conflicts of interest are found at the end of this article

Correspondence to: Charise Gleason, MSN, NP-BC, AOCNP®, Winship Cancer Institute of Emory University, 1365 Clifton Road, NE, Atlanta, GA 30322. E-mail: charise.gleason@emoryhealthcare.org

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As treatment for myeloma continues to evolve, one of the most promising groups of agents in development are monoclonal antibodies (MAbs). MAb-based therapy, which has been used in other types of cancers for many years, works by targeting diverse cell-surface antigens. MAbs are able to damage tumor cells through several mechanisms of action: direct elimination of tumor cells, indirect immune-mediated targeting of cancer cells, and targeting of tumor stroma and vasculature (Allegra et al., 2013; Richardson, Lonial, Jakubowiak, Harousseau, & Anderson, 2011; Scott, Wolchock, & Old, 2012; Tai & Anderson, 2011; Van De Donk, Kamps, Mutis, & Lokhorst, 2012).

Direct cytotoxicity occurs with MAbs by targeting signaling pathways, or by acting as carriers of chemotherapeutics or radioisotopes (Allegra et al., 2013; Scott et al., 2012; Van De Donk et al., 2012; Tai & Anderson, 2011; Richardson et al., 2011). MAbs can also induce tumor cell kill by indirect mechanisms mediated by the immune system, which includes antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). ADCC is activated by interactions between the Fc region of MAbs bound to the tumor cell and Fc receptors on immune effector cells (e.g., T cells and B cells, natural killer [NK] cells), inducing cytotoxicity by immune cells (Allegra et al., 2013; Scott et al., 2012). CDC is triggered by interactions between the Fc region of MAb with the C1q component of the complement pathway, resulting in the accumulation of C3b and subsequent formation of the membrane attack complex (Allegra et al., 2013; Richardson et al., 2011; Scott et al., 2012; Tai & Anderson, 2011; Van De Donk et al., 2012). Two MAbs, elotuzumab and daratumumab, have been recently approved by the US Food and Drug Administration (FDA) for use in the treatment of MM. Elotuzumab is a immunostimulatory antibody that targets a cell-surface glycoprotein, signaling lymphocyte activating molecule (SLAM-F7). Daratumumab is an anti-CD38 monoclonal antibody. Both drugs will be discussed below in more detail.

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DARATUMUMAB

Indication

Daratumumab (Darzalex; DARA) is a human CD38-directed MAb indicated for the treatment of patients with MM who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials (Janssen Biotech, 2015). Daratumumab was granted FDA approval on November 16, 2015.

Formulation

Intravenous formulation: 100 mg/5 mL solution in a single-dose vial, or 400 mg/20 mL solution in a single-dose vial.

Pharmacology/Mechanism of Action

Daratumumab is a fully human MAb that binds to glycoprotein CD38, which is overexpressed on MM cells (Lonial et al., 2015a). Once bound, the antibody interacts with NK cells by mimicking the normal interaction between CD38 and CD31. This interaction elicits ADCC and CDC, resulting in antitumor activity (de Weers et al., 2011; Groen et al., 2010; Overdijk et al., 2012). DARA has been used in clinical trials as monotherapy and in combination with other novel agents (Lonial et al., 2015a). See Figure 1 for an illustration of daratumumab's mechanism of action.

Dosing and Administration

The FDA-approved dosing for DARA is based on preclinical and clinical pharmacokinetic (PK) data. The approved dose is 16 mg/kg IV weekly for weeks 1 to 8, then every 2 weeks for weeks 9 to 24, then every 4 weeks from week 25 onwards until disease progression. DARA is currently being investigated in studies in combination with lenalidomide, pomalidomide, or bortezomib.

Clinical Trials: Efficacy and Safety

DARA has been shown to be effective as a single agent but is especially effective in combination with lenalidomide and dexamethasone. An overall response rate (ORR) of 29.2% (95% confidence interval [CI] = 20.8%–38.9%) was demonstrated in the MMY2002 (SIRIUS) study, an open-label phase II pivotal trial, using daratumumab as a single agent in patients with a median of 5 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent (Janssen Biotech, 2015). The median duration of response was 7.4 months (range, 1.2 to 13.1+ months; Lonial et al., 2015b).

In a trial of 30 patients, all demonstrated marked decrease in M-protein (Plesner et al., 2014), with a median time to response of 4.3 weeks (range, 2.1 to 11.3 months) and ORR of 75% (15 out of 20 patients). In other studies, newly diagnosed patients were treated with DARA/bortezomib/dex, bortezomib/melphalan/prednisone, or bortezomib/thalidomide/dex, with all patients achieving at least a partial response (PR). In a study evaluating 24 patients with relapsed/refractory MM (RRMM), DARA, pomalid-

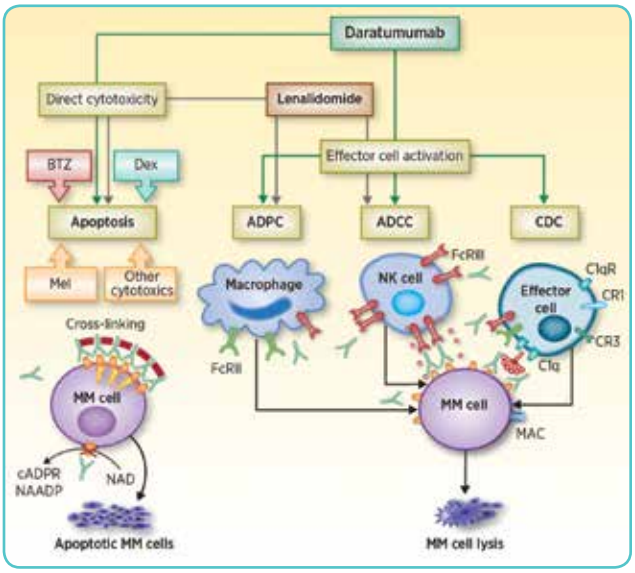

Figure 1. The mechanism of action of daratumumab includes immunomodulatory effects. ADCC = antibody-dependent cell-mediated cytotoxicity; ADPC = antibody-dependent cellular phagocytosis; AMP = adenosine monophosphate; Breg = regulatory B cell; Ca2+ = calcium ion; cADPR = cyclic adenosine diphosphate-ribose; CDC = complement-dependent cytotoxicity; DARA = daratumumab; MDSC = myeloid-deprived suppressor cell; MM = multiple myeloma; NAADP = nicotinic acid adenine dinucleotide phosphate; NAD = nicotinamide adenine dinucleotide; Treg = regulatory T cell.

omide, and dex used in combination resulted in an ORR of 55% in the 11 patients available for efficacy assessment (Mateos et al., 2015).

The most common adverse event (AE) reported with DARA included grade 1/2 infusion reactions, most often during the first infusion (Lonial et al., 2015b; Mateos et al., 2015; Plesner et al., 2014). Thrombocytopenia, anemia and pneumonia are the most common grade 3/4 AEs (Lokhorst et al., 2014; Lonial et al., 2015b).

Implications for the Advanced Practitioner and Recommended Supportive Care

Premedication with a corticosteroid, acetaminophen, and diphenhydramine is recommended to reduce the incidence and severity of infusion reactions. Premedication with an antiemetic is recommended to reduce the incidence of nausea and vomiting. Clinical monitoring for cytopenias, hepatic and renal abnormalities should be conducted at baseline and regularly during treatment. Laboratory analysis should include a baseline type and screen for packed red blood cells. Daratumumab binds to CD38, a protein that is ubiquitously expressed on myeloma cells but also expressed, to a lesser extent, on red blood cells (RBCs). Daratumumab interferes with the indirect Coombs test by binding to endogenous CD38 on RBCs, resulting in panagglutination. Blood banks should be notified that they will receive a daratumumab-treated patient sample to prevent a delay in the release of blood products. Procedures may vary among institutions. No specific data on the use of DARA in the elderly or special populations has been reported. Steroids such as dexamethasone should be administered in lower doses in the elderly (Palumbo et al., 2014).

ELOTUZUMAB

Indication

Elotuzumab (Empliciti; ELO) is indicated in combination with lenalidomide and low-dose dexamethasone in the treatment of multiple myeloma in patients who have received 1 to 3 prior medications (Bristol-Myers Squibb, 2015).

Formulation

Intravenous formulation.

Pharmacology/Mechanism of Action

Elotuzumab is a MAb that targets myeloma cells expressing signaling lymphocyte activation family 7 (SLAMF-7, also called CS1). CS1 is a cell-surface glycoprotein molecule that is highly expressed on myeloma cells at the gene and protein level, but not on other tissues (Tai et al., 2008). CS1 protects myeloma cells from undergoing apoptosis by regulating several signaling pathways (Tai et al., 2008), and regulates NK cell activity by recruiting additional signaling pathways (Tassi & Colonna, 2005). Elotuzumab targets the surface adhesion molecule CS1, resulting in the inhibition of stimulatory effects of bone marrow on MM survival and proliferation (Tai et al., 2008).

In preclinical studies, ELO induces NK-mediated myeloma cell death, with minimal effect on normal cells (Balasa et al., 2015; Figure 2). The SLAM family, comprised of six receptor molecules located on chromosome 1q23, includes SLAM, 2B4, Ly-9, NTB-A, CD94, and SLAMF7 (Cannon, Tangye, & Schwatz, 2011). More than 95% of bone marrow myeloma cells express SLAMF7 in a manner that is independent of cytogenetic abnormalities (Tai et al., 2008).

Dosing and Administration

The approved indication is based on the registrational phase III ELOQUENT-2 trial combining ELO, lenalidomide, and low-dose dexamethasone (ERd). Dosing for the ERd regimen includes ELO 10 mg/kg given IV on days 1, 8, 15, and 22 for cycles 1 to 2 and on days 1 and 15 for subsequent cycles; oral lenalidomide (25 mg; days 1–21); and oral dexamethasone (28 mg plus 8 mg IV on ELO dosing days, or 40

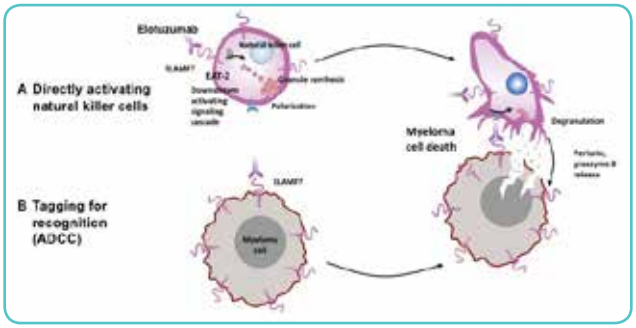

Figure 2. Elotuzumab: Immunostimulatory mechanism of action. ADCC = antibody-dependent cell-mediated cytotoxicity; SLAMF7 = signaling lymphocytic activation molecule F7.

mg once weekly). ELO was infused in the trial at up to 2 mL/min for cycles 1 to 4 and could be escalated up to 5 mL/min for subsequent cycles.

Clinical Trials: Efficacy and Safety

A phase III study (ELOQUENT-2) investigating ELO in combination with lenalidomide and dexamethasone (ERd) (NCT01239797; Lonial et al., 2015c) randomized patients with RRMM (1–3 prior therapies) who were not refractory to lenalidomide to receive ERd or standard lenalidomide-dexamethasone (Rd) in 28-day cycles. Treatment was continued until disease progression or unacceptable toxicity. The primary endpoints were progression-free survival (PFS) and ORR. At interim analysis, 646 patients had been enrolled (321 ERd, 325 Rd). A number of patients in this trial had adverse disease attributes, including del(17p) in 32% and t(4;14) in 9%.

At 24 months of follow-up, patients in the ERd arm demonstrated a 30% reduction in the risk of disease progression or death compared to the Rd alone arm, for a hazard ratio (HR) of 0.70 (95% CI = 0.57–0.85); p = .0004; Empliciti prescribing information). Similarly, PFS favored ERd over Rd, with a median of 19.4 (16.6–22.2) months versus 14.9 (12.1–17.2) months and HR of 0.70 (95% CI = 0.57–0.85; p = .0004). At 2 years of follow-up, 35% (ERd) and 21% (Ld) of patients remained on therapy; discontinuation was mainly for disease progression (42% ERd, 47% Rd). The most common reason for discontinuation of therapy was disease progression.

The most common adverse events (AEs) of grade 3 or greater reported in at least 10% of patients in the ELOQUENT-2 trial (ERd vs. Rd) included lymphopenia (76.7% vs. 48.7%), leukopenia (32.4% vs. 25.6%), thrombocytopenia (19.2 % vs. 20.3%), hyperglycemia (17.0% vs. 10.2%), pneumonia (14.2% vs. 9.5%), and fatigue 12.6% vs. 11.7%). Among the most common AEs of all grades were fatigue (61.6% vs. 51.7%), diarrhea (46.9% vs. 36%), pyrexia (37.4% vs. 36%), constipation (35.5% vs. 27.1%), and cough (34.3% vs. 18.9%). Infusion reactions were reported in 10% of patients, with only 1% at grade 3. The majority of infusion reactions occurred with the first dose (70%), and the majority of patients were able to continue the infusion after administration of additional medications and an interval of 25 minutes.

Implications for the Advanced Practitioner and Recommended Supportive Care

Similar to other MAbs used in the treatment of hematological malignancies, patients receiving ELO should receive premedications with antihistamines and corticosteroids to mitigate infusion reactions. In addition, a hypersensitivity reaction protocol should be in place to allow for immediate management of any reactions; these generally include parameters for stopping the infusion and administering additional medications while awaiting for the provider to arrive (Lieberman et al., 2010). Importantly, the AE profile for ERd is based on combination therapy, so the AE profile of all agents in this regimen must be considered. Therefore, prophylaxis for VTE and pneumococcal infections should be provided. Patients with diabetes or a history of hyperglycemia will need to be monitored closely. Infection prophylaxis for shingles should be considered, and all patients should receive concurrent supportive and palliative care as described by Richards and Brigle (2015). Laboratory monitoring should include a CBC with differential and complete metabolic panel. Importantly, ELO is an IgG kappa monoclonal antibody and may interfere with monitoring of disease response or progression. The timing of testing for IgG or kappa light chain MM should be considered.

Disclosure

Ms. Charise Gleason has acted as a consultant for Celgene Corporation and Takeda Oncology. Ms. Hollie Devine has no potential conflicts of interest to disclose. Dr. Beth Faiman has acted as a consultant, a lecturer, and served on speakers bureaus for Celgene Corporation, Takeda Oncology, and Amgen. Ms. Deborah Doss has acted as a consultant for Celgene Corporation, Takeda Oncology, Amgen, and Bristol-Myers Squibb Company, and acted as a lecturer and served on speakers bureaus for Celgene Corporation, Takeda Oncology, and Amgen. Ms. Sandra Kurtin has received honoraria from and acted as a consultant for Celgene Corporation, Takeda Oncology, Amgen, Bristol-Myers Squibb Company, and Novartis International AG. Members of the International Myeloma Foundation Nurse Leadership Board served as reviewers for this work. The authors are solely responsible for the content.

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