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Immunotherapy for the treatment of multiple myeloma

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ABSTRACT

Immunotherapy has recently emerged as a promising treatment for multiple myeloma (MM). There are now several monoclonal antibodies that target specific surface antigens on myeloma cells or the checkpoints of immune and myeloma cells. Elotuzumab (targeting SLAMF7), daratumumab (targeting CD38), and pembrolizumab (targeting PD-1) have shown clinical activity in clinical studies with relapsed/refractory MM. Dendritic cell vaccination is a safe strategy that has shown some efficacy in a subset of myeloma patients and may become a crucial part of MM treatment when combined with immunomodulatory drugs or immune check-point blockade. Genetically engineered T cells, such as chimeric antigen receptor T cells or T cell receptor-engineered T cells, have also shown encouraging results in recent clinical studies of patients with MM. In this paper, we discuss recent progress in immunotherapy for the treatment of MM.

1. Introduction

Multiple myeloma (MM) is an incurable B-cell malignancy characterized by the aberrant expansion of clonal malignant plasma cells into bone marrow that eventually causes renal failure, anemia, infection, and osteolytic bony lesions (Kyle and Rajkumar, 2004). MM accounts for 1% of all cancers and more than 10% of all hematological malignancies in the United States (Siegel et al., 2015). The incidence of MM in Korea has rapidly increased in recent years (Lee et al., 2010). The prognosis for patients with MM has improved with the development of novel effective agents, and median survival has increased to approximately 6 years (Kumar et al., 2014). However, most patients with MM eventually relapse and develop resistance to their treatments. New therapies that increase the response and survival rates with minimal toxicity are needed.

Immunotherapy has recently emerged as a promising treatment for many cancers. In MM, the efficacy of immunotherapy is based on the observation that allogenic stem cell transplantation is curative

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Table 1
Monoclonal antibodies and their targets in multiple myeloma.

CD38	Daratumumab, Isatuximab, MOR202
SLAMF7	Elotuzumab,
CD56	Lorvotuzumab
PD-1	Pembrolizumab, Pidilizumab, Nivolumab
CD138	Indatuximab
CD40	Dacetuzumab
CXCR4	Ulocuplumab
FGFR3	MFGR1877S

for a subset of patients with MM due to the graft-versus-myeloma (GVM) effect (Tricot et al., 1996). In addition, the GVM effect is supported by disease response following donor lymphocyte infusions (Bellucci et al., 2004). However, allogenic stem cell transplantation does not have specific immune activity for myeloma cells and is associated with significant morbidity and mortality, including graft-versus-host disease. Therefore, investigators have focused on developing new tools to elicit myeloma-specific immune responses. An example of a new immunotherapeutic strategy is the development of a monoclonal antibody(mAb)-targeting surface antigen on myeloma cells (Table 1). Daratumumab, targeting CD38 and elotuzumab, targeting signaling lymphocyte activation molecule F7 (SLAMF7), have shown clinical activity in monotherapy or combination therapy with other agents in clinical studies. In addition, cellular immunotherapy using dendritic cell (DC) vaccination and adoptive immunotherapy with chimeric antigen receptor (CAR) T cells or T cell receptor (TCR)-engineered T cells are emerging as promising treatment strategies for MM.

This review focuses on recent preclinical and clinical data from the dominant mAbs, DC vaccine, and genetically engineered T cell therapies for MM.

2. Monoclonal antibodies

2.1. Elotuzumab

Elotuzumab is a first-in-class humanized IgG1 immunostimulatory mAb targeted to SLAMF7. It is also referred to as cell surface glycoprotein CD2 subset 1 (CS1), SLAMF7 is a glycoprotein expressed on myeloma cells and natural killer (NK) cells but not on normal tissue (Wang et al., 2016). It may play an important role in the interaction between myeloma cells and their adhesion to bone marrow stromal cells, which contributes to the survival and growth of myeloma cells. In addition, it plays an important role in NK cell activation (Cruz-Munoz et al., 2009). The mechanisms of the antitumor effects of elotuzumab include disrupting MM cell adhesion to bone marrow stromal cells, enhancing NK cell cytotoxicity, and mediating antibody-dependent cell-mediated cytotoxicity (ADCC), but not complement-mediated cytotoxicity (CDC).

In a phase I study, elotuzumab was well tolerated in patients with advanced MM (Zonder et al., 2012). The most common adverse event was grade 1 or 2 infusion-related reaction, and 58.8% of patients experienced an infusion reaction during the first elotuzumab infusion. Although 26.5% of patients achieved disease stabilization, objective clinical responses were not seen with elotuzumab monotherapy. A clinical study of combination treatments with other approved drugs has been conducted, because elotuzumab showed encouraging anti-myeloma activity in preclinical studies when in combination with other agents (Tai et al., 2008; van Rhee et al., 2009). In a phase I study that evaluated the safety and efficacy of elotuzumab, lenalidomide, and dexamethasone in relapsed or refractory patients with MM, combination treatment resulted in a higher response rate (at least partial response, 82%) (Lonial et al., 2012), which compared favorably with the historical response rate of 60% using lenalidomide and dexamethasone (Dimopoulos et al., 2007). These favorable results may be due to the synergistic activity of the two drugs: elotuzumab acts primarily through NK cell-mediated ADCC, and lenalidomide increases the number and anti-MM cytotoxic activity of NK cells. A phase II study also reported that the overall response rate was 84%, including 42% with a very good partial response (VGPR), and treatment was generally well tolerated (Richardson et al., 2015). In a randomized phase III study (ELOQUENT-2), patients treated with elotuzumab plus lenalidomide and dexamethasone had a higher response rate than patients treated with lenalidomie and dexamethasone (79% vs. 66%, $P < 0.001$), without a significant increase in adverse events. The median progression free survival (PFS) in the elotuzumab arm was 19.4 months, compared to 14.9 months in the lenalidomide/dexamethasone arm (Lonial et al., 2015).

Bortezomib also enhanced the activity of elotuzumab in a preclinical study (van Rhee et al., 2009). In a phase I study, elotuzumab and bortezomib were well tolerated in patients with relapsed or refractory MM, with an overall response rate of 48% and median time to progression of 9.5 months (Jakubowiak et al., 2012). In a phase II study that evaluated the efficacy and safety of elotuzumab with bortezomib and dexamethasone compared to boretezomib and dexamethasone, median PFS was longer in the elotuzumab arm than the control arm (9.7 months vs. 6.9 months, $P = 0.09$). The overall response rate was also higher in the elotuzumab arm (66% vs. 63%) (Jakubowiak et al., 2016).

2.2. Daratumumab and other monoclonal antibodies targeting CD38

Daratumumab is a first-in-class human anti-CD38 IgG1k mAb. CD38 is a 45 kDa transmembrane glycoprotein that is highly expressed on malignant plasma cells, but is expressed at relatively low levels on normal lymphoid and myeloma cells (de Weers et al., 2011). Daratumumab binds CD38 on myeloma cells and induces cell death through several immune-mediated mechanisms, including CDC, ADCC, antibody-dependent cell phagocytosis (ADCP), induction of apoptosis, and modulation of CD38 enzyme activity (Overdijk et al., 2015). In addition, a recent study showed that daratumumab has immune-modulating effects through the reduction of $CD38^+$ immunosuppressive cells and an increase in $CD8^+$ cytotoxic T cells and $CD4^+$ helper T cells in patients with relapsed or refractory MM (Krejcik et al., 2016).

A previous phase I/II study (GEN501) utilized a 3 + 3 dose-escalation design with daratumumab administration, that ranged from 0.005 to 24 mg per kg of body weight (Lokhorst et al., 2015). The maximum tolerated dose was not reached with the use of doses up to 24 mg/kg. In patients treated with a dose of 16 mg/kg, the overall response rate was 36%. The median PFS was 5.6 months, and the overall survival (OS) rate at 12 months was 77%. The SIRIUS study reported similar results (Lonial et al., 2016). Overall responses were noted in 29.2% of patients treated with 16 mg/kg. Furthermore, at least a partial response (PR) was achieved in 21% of patients who were refractory to four drugs (bortezomib, lenalidomide, pomalidomide, and carfilzomib). These data suggest that resistance to previous therapy did not affect the activity of daratumumab. The median PFS was 3.7 months, and the 12-month OS was 64.8%. Daratumumab treatment was generally safe, and most of the common non-hematological adverse events were infusion-related reactions, such as fever, cough, nausea, dizziness, and bronchospasm. Most infusion-related reactions occurred in the first infusion, and the infusion rate may be associated with the development of infusion-related reactions.

In an *in vitro* study, combinations of daratumumab and lenalidomide significantly increased lysis of MM cells, mainly due to the potent capacity of lenalidomide to activate ADCC effector cells (van der Veer et al., 2011b). In addition, bortezomib enhanced the ther-