Immunotherapy in myeloma: Why, when and how?

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**Abstract**

Monoclonal antibodies targeting cell surface antigens, such as SLAMF7 and CD38, have multiple modes of action including classic Fc-dependent effector mechanisms such as antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP). In addition, immunomodulatory activity has also been described for elotuzumab (NK cell activation) and daratumumab (elimination of immune suppressor cells, and T cell expansion). CD38-targeting antibodies have single agent activity, while elotuzumab has no activity as monotherapy in heavily pretreated patients. Both CD38- and SLAMF7-targeting antibodies are active in combination with various standards of care, and have transformed treatment of relapsed/refractory MM patients. It is expected that incorporation of these agents in the treatment of newly diagnosed MM, will further improve outcome of MM patients. Other immunotherapeutic agents with different modes of action, such as bispecific antibodies, PD1/PD-L1 blocking agents, antibody-drug-conjugates, and CAR T cells will further enhance our armamentarium against MM, and contribute to further improvements in survival of MM patients.

**Introduction**

The outcome of newly diagnosed MM patients has markedly improved with the introduction of novel agents such as immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs). However, survival of patients with poor-risk cytogenetic abnormalities is poor, and also outcome of patients who become refractory to IMiDs and PIs is dismal. Therefore, new anti-MM agents with novel mechanisms of action are needed to further improve outcome. In this respect, various types of immunotherapy have already transformed MM treatment in the past few years, or are very promising to do the same in the nearby future. In my presentation, I will discuss the biological and clinical data of currently approved immunotherapies such as elotuzumab and daratumumab. Also the most promising new immunotherapeutic agents in advanced phases of clinical testing will be discussed.

**Current state-of-the-art**

**Allogeneic stem cell transplantation**

The first immunotherapeutic approach used in the treatment of MM is allogeneic stem cell transplantation (allo-SCT), which has the potential of inducing durable remissions by virtue of the graft-versus-myeloma effect mediated by donor T cells. However, because of high treatment-related mortality, and the introduction of novel forms of immunotherapy, which are effective with relatively mild toxicity, the role for allo-SCT in MM is currently decreasing. Allo-SCT can be considered in patients with early relapse after autologous stem cell transplantation and in primary plasma cell leukemia after successful novel agent-containing (re)induction therapy in the context of clinical trials.

**Monoclonal antibodies targeting surface antigens on the MM cell**

SLAMF7, a member of the immunoglobulin gene superfamily, is highly expressed on normal and malignant plasma cells, as well as on NK cells. The SLAMF7-targeting antibody elotuzumab induces MM cell death via antibody-dependent cellular cytotoxicity (ADCC) and also activates NK cells, but has no single agent activity in extensively pretreated MM patients. However, in the Eloquent-2 study there was a marked improvement in PFS and trend towards improved OS when elotuzumab was added to lenalidomide-dexamethasone (Rd) as compared to Rd alone. The ongoing Eloquent-3 study is evaluating pomalidomide-dexamethasone with or without elotuzumab in relapsed/refractory MM. Elotuzumab is also evaluated in newly diagnosed MM: both in transplant ineligible patients (e.g., Eloquent-1 study; Rd with or without elotuzumab) and in transplant eligible patients (e.g., GMMG-HD6; elotuzumab plus RVD in induction and consolidation, as well as during maintenance in combination

**Take Home Messages**

- Monoclonal antibodies targeting cell surface antigens have classic Fc-dependent effector mechanisms.
- CD38-targeting antibodies and elotuzumab also have immunomodulatory effects.
- CD38-targeting antibodies have single agent activity.
- CD38-targeting antibodies and elotuzumab combine well with standards of care for MM treatment.
- Preliminary results from new immunotherapeutic agents such as bispecific antibodies, antibody-drug conjugates, and CAR T cells are promising.
with lenalidomide). The elotuzumab plus Rd combination is also evaluated in smoldering MM, with promising preliminary results.6

**CD38 antibodies: daratumumab, isatuximab, and MOR202**

CD38 is a transmembrane glycoprotein with ectoenzymatic activity, and also functions as a receptor and adhesion molecule. CD38 is highly expressed on normal and malignant plasma cells, but also on other lymphoid and myeloid cells, as well as tissues of nonhematopoietic origin such as prostate epithelial cells, pancreatic islet cells, airway-striated muscle cells, renal tubule cells, retinal ganglial cells, corneal cells, as well as perikarya and dendrites of some neurons. Although CD38 has a relatively broad tissue distribution, CD38 antibodies (daratumumab, isatuximab, and MOR202) have a remarkably favorable toxicity profile mainly consisting of infusion reactions which predominantly occur during the first infusion.7 CD38 antibodies induce MM cell death via Fc-dependent immune effector mechanisms including complement-dependent cytotoxicity (CDC), ADCC, and antibody-dependent cellular phagocytosis (ADCP). CD38 antibodies also have direct effects such as modulation of CD38 enzymatic function. Interestingly, daratumumab treatment results in rapid reduction of CD38 surface expression on the tumor cells, both in responding and non-responding patients, which is mediated by selection of cells with lower CD38 expression and by trogocytosis (transfer of antibody-CD38 complexes from the tumor cell to granulocytes and monocytes).8 Since the target antigen was rapidly reduced, also in patients with ongoing and deepening responses, we evaluated whether daratumumab also has other modes of action. Indeed, we found that daratumumab eliminates CD38-positive immune suppressor cells such as regulatory T cells, regulatory B cells, and myeloid-derived suppressor cells (MDSCs). This shift away from an immunosuppressive microenvironment results in CD4+ and CD8+ T cell expansion, and potentially a better host-anti-tumor immune response.9

Although, the relative contribution of these different mechanisms of action varies among the three CD38 antibodies, they have similar efficacy as monotherapy in advanced myeloma (at least PR in approximately 30% of patients).10,11 CD38 antibodies also perform well in combination with other standards of care, such as Rd, velcade and dexamethasone (Vd), and pomalidomide-dexamethasone (Pd).12-15 Daratumumab is currently approved by EMA and FDA as monotherapy in relapsed/refractory myeloma, and in combination with Rd and Vd in patients with at least one prior line of therapy. The FDA also approved daratumumab in combination with Pd for the treatment of MM patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor. Based on the high activity and favorable toxicity profile, CD38 antibodies are currently also evaluated in newly diagnosed MM patients.12 The interim results from the ALCYONE study showed that adding daratumumab to bortezomib-melphanal-prednisone (VMP), which is one of the standards of care for patients ineligible for transplant, improved response rates and PFS, when compared to VMP alone.16 The MAIA study is evaluating the added value of daratumumab plus Rd in patients who are not eligible for transplant. Other studies are evaluating whether daratumumab in induction, consolidation, and maintenance also improves the outcome in younger, transplant eligible patients (e.g., Cassiopeia study; daratumumab with VTD in induction and consolidation, and as maintenance). Furthermore, preliminary results from the CENTAURUS study show promising activity of daratumumab as single agent in high-risk smoldering MM. Importantly, although CD38 antibodies are well tolerated, they interfere with blood transfusion tests as these antibodies bind to CD38-positive test red blood cells.17 However, several mitigation strategies can be applied to safely and timely provide blood products for patients treated with CD38 antibodies.

**Antibody-drug conjugates**

Various antibody-drug conjugates (ADC) were previously tested in clinical trials in MM including ADCs targeting CD56 and CD138. Another promising ADC is GSK2857916, which is a BCMA-targeting antibody conjugated to the auristatin analogue and microtubule inhibitor monomethyl auristatin phylanline (MMAf). Preliminary results show high activity in relapsed/refractory MM patients with a 60% overall response rate including CRs.18 Corneal toxicity was specifically associated with GSK2857916. Based on these results the FDA recently granted GSK2857916 a breakthrough therapy designation for patients with relapsed/refractory MM.

**PD1 and PD-L1 inhibitors**

In the immunosuppressive MM microenvironment, PD-L1 is frequently upregulated on tumor cells and PD1 on effector cells. Binding of PD1 to PD-L1 results in impaired T cell or NK cell function, and may contribute to immune escape and tumor growth. Therefore, antibody blockade of the PD1/PD-L1 pathway is currently investigated in MM patients. PD1/PD-L1 neutralizing antibodies have no single-agent activity in MM, but phase 1 and 2 studies showed that the combination of the PD-1 inhibitor pembrolizumab with lenalidomide or pomalidomide was effective.19 However, unexpectedly, in the summer of 2017 an increased risk of death was seen in the pembrolizumab plus IMiD arm in two phase 3 studies. In relation to risks identified in these studies, the FDA put a (partial) clinical hold on studies evaluating PD1 and PD-L1 inhibitors in MM. In the end of 2017 the clinical hold was lifted for several studies evaluating these checkpoint inhibitors plus other drugs, but not for combinations with IMiDs. Preclinical data suggests that PD1 and PD-L1 blockers may be effective partners with elotuzumab or CD38 antibodies, but results from these ongoing clinical studies have to be awaited.7

**Bispecific antibodies, Bi-specific T-cell engagers (BITES), and CAR T cells**

Because the endogenous host-anti-tumor immune response is not enough to eliminate MM, therapies are also designed to redirect T cells to MM cells. This can be done by engineering the cells ex vivo, such as in CAR T cell therapy, or in vivo, such as with bispecific antibodies. Bispecific antibodies recognize two different epitopes. The BCMAxCD3 antibody redirects the cytotoxic activity of T cells by binding to CD3 and a tumor-associated antigen (BCM). Preclinical results with these BCMAxCD3 antibodies are promising and formed the rationale for currently ongoing phase 1 studies in relapsed/refractory MM.20 BiTEs are fusion proteins consisting of two single-chain variable fragments (scFvs) of different antibodies. Several BiTEs are currently being evaluated either preclinically or clinically. Similar to bispecific antibodies, CAR T cells can also redirect T cells to kill MM cells without human leucocyte antigen (HLA)-restriction (Figure 1A).21 CAR T cells are also promising in MM, with high activity of anti-BCMA CAR T cells in extensively pretreated patients (Figure 1B for details on trials evaluating BCMA-targeted CAR T cells). However, more has to be learnt about long-term efficacy and management of toxicity.

**Future perspectives**

Antibodies targeting cell surface antigens have a different mode of action when compared to IMiDs and PIs, and are well tolerated, which makes them attractive partners in combination with
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Figure 1. CAR T cells are promising as new treatment strategy in MM. A) CAR T cells redirect T cells to kill MM cells without human leucocyte antigen (HLA)-restriction. B) Characteristics of trials evaluating BCMA-targeted CAR T cells in MM. Abbreviations: Ag, antigen; NA, not available; scFv, single-chain variable fragment; Flu, fludarabine; Cy, cyclophosphamide; PR, partial response; CR, complete response; sCR, stringent complete response; CRS, cytokine-release syndrome.
standards of care. Indeed, in the relapse setting antibody-based triplets are among the most active regimens that are currently available. It is therefore expected that addition of daratumumab or elotuzumab to induction, consolidation, and maintenance will also improve the outcome of both younger and elderly patients with newly diagnosed MM. Bispecific antibodies, checkpoint inhibitors, antibody-drug conjugates, and CART cells have different modes of action and have shown promising activity in relapsed/refractory MM. It is expected that these agents will contribute to further improvements in MM survival.

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