Monoclonal Antibodies in Multiple Myeloma

Subjects: Oncology

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Multiple myeloma is the second most common hematologic malignancy. Current treatment strategies are mainly based on immunomodulatory drugs, proteasome inhibitors or combination of both. Monoclonal anti-CD38 antibodies, daratumumab and isatuximab, have been implemented into treatment strategies from first-line treatment to refractory disease. In addition, the monoclonal anti-SLAM-F7 antibody elotuzumab in combination with immunomodulatory drugs has improved the clinical outcomes of patients with relapsed/refractory disease. Belantamab mafodotin is the first approved antibody drug conjugate directed against B cell maturation antigen and is currently used as a monotherapy for patients with advanced disease.

Keywords: multiple myeloma ; monoclonal antibodies ; antibody drug conjugates

1. Introduction

Multiple myeloma (MM) is a clinically heterogeneous disease, as evidenced by considerable variation in rates of response to treatment and overall survival (OS); indeed, OS in patients with MM has been shown to range from a few months to more than a decade [1]. MM has long represented a therapeutic challenge. After introduction of proteasome inhibitors and immunomodulating agents, the landscape of treatment is still rapidly evolving, and monoclonal antibodies (MoAb) have become an integral part of the myeloma therapeutic approach. Myeloma cells carry several potential targets for immunotherapy with CD38 and B cell maturation antigen (BCMA) being the most widely studied.

2. CD38

CD38 is a transmembrane glycoprotein first described more than 40 years ago in 1980 as a marker of T cell differentiation [2]. The molecule is expressed and distributed not only on plasma cells but also on other myeloid and lymphoid cells [3]. High expression of CD38 can be observed on natural killer (NK) cells and subsets of T lymphocytes [4]. Other immune effector cells also show high expression of CD38 including regulatory B cells and antigen presenting cells (APC), especially plasmacytoid dendritic cells. A decrease in plasmacytoid densdritic cells, which support MM cell growth and survival, may represent another potent immune effect of CD38 antibodies [5][6]. CD38 works as an enzyme (ectoenzyme) at it also can serve as a receptor triggering proliferation signals [7]. As an enzyme, it is involved in the catabolism of nicotinamide adenine dinucleotide (NAD+) and nicotinamide adenine dinucleotide phosphate (NADP). Some studies suggest that CD38 is involved in the production of adenosine. MM cells grow in an environment rich with adenosine and levels of adenosine are higher in the bone marrow of MM patients compared to patients with monoclonal gammopathy of undetermined significance [8]. It was recently reported that so called mitochondrial transfer from stromal plasma cells to malignant MM cells via the tumor-derived tunneling nanotubes is facilitated by CD38 molecules which leads to enhancement of MM cells energy sources [9]. Other functions of CD38 were demonstrated in CD38 knockout mouse models. For example, loss of CD38 makes mice susceptible to bacterial infections due to impaired neutrophil migration [10]. In addition, CD38 regulates the migration of dendritic cell precursors from the blood to peripheral sites [11].

3. Anti-CD38 Monoclonal Antibodies

Several MoAbs targeting CD38 are currently available for MM treatment either as approved drugs (daratumumab and isatuximab) or still in clinical development (MOR202 and TAK-079). Daratumumab, a fully human IgG1-k antibody, was the first approved antibody for the treatment of MM patients, briefly followed by isatuximab (chimeric IgG1-k antibody), and MOR202, fully human IgG1-l antibody was studied in phase I/II clinical trial but to date, no other trials are ongoing in MM [12]. TAK-079 (fully human monoclonal antibody) binds to CD38 with high affinity and currently two clinical trials in MM are ongoing) [13].

4. Anti SLAMF-7 Monoclonal Antibodies

Signaling Lymphocyte Activation Molecule Family 7 (SLAMF-7) is a consistently expressed glycoprotein on the surface of MM cells. SLAMF7 is also expressed on lymphocytes, especially NK cells, activated T cells, and most B cells [14][15][16]. The SLAM family receptors play important roles in immune regulation. SLAMF-7 works in cooperation with Ewing's sarcoma-associated transcript 2 (EAT-2). SLAMF-7 together with EAT-2 triggers activating NK cell signals thereby increasing NK cell activity [14][17]. It is important to note that MM cells lack EAT-2 so SLAMF-7 does not provide activation signals. Soluble SLAMF-7 acts as a growth factor for MM cells [18]. Additionally, increase in soluble SLAMF-7 may point to disease progression [19]. Elotuzumab is a humanized monoclonal IgG1 antibody that binds SLAMF7 and is currently approved for treatment of patients with RRMM. Tagging of MM cells and increase in the activity of NK cells is probably the explanation of mechanism of action of elotuzumab. It promotes NK cell dependent ADCC [20]. It lacks other mechanisms of action typical for other MoAbs such as CDC [21]. ADCP activity of elotuzumab has been recently documented in a xenograft MM mouse model [22].

5. Antibody Drug Conjugates

Antibody drug conjugates (ADC) represent an attractive approach to treat various hematologic malignancies [23]. After successful introduction of brentuximab vedotin for the treatment of Hodgkin lymphomas and T cell lymphomas and significant success of revived gemtuzumab ozogamicin in acute myeloid leukemia, myeloma has gained its desired attention with ADCs too [24][25]. The basic idea of these drugs is to deliver the cytotoxic drug (referred to as a payload) directly to the malignant cells. The payload is usually linked to a MoAb via a linker which is noncleavable in the circulation and the release of payload is secured by the degradation of the antibody in lysosome. The antibody is usually internalized via endocytosis and then processed by natural cellular processes leading to cleavage of the linker and release of the payload, and finally killing of the malignant cell. The most challenging issue in ADCs is the selection of target membrane protein [26]. The target should optimally be highly expressed on malignant cells and not be present on other cells to limit the toxicity to normal tissues. It is obvious that such targets are difficult to find. Several targets in MM cells were suggested: BCMA, CD56, CD138, and potentially some others like CD74. The toxins attached to MoAb are usually small cytotoxic molecules seldom used as systemic chemotherapy because of adverse toxic profiles. These drugs (as would be expected from chemotherapeutic agents) cause DNA damage or cell cycle cessation. Calicheamicins or pyrrolobenzodiazepine dimers represent DNA damage mechanism and auristatin derivates (monomethylauristatin F) belong to the group of microtubule inhibitors [27][28].

Out of all possible targets, BCMA has gained the most attention among all other targets. BCMA is beside myeloma cells, only expressed on plasmablasts and mature plasmacytes which makes it an attractive target. BCMA has two known ligands: B-cell activating factor (BAFF) and A Proliferation-Inducing ligand (APRIL). Activation of BCMA leads to activation of NF kappa B pathways creating a prosurvival signal. Results of this process include proliferation, differentiation, and longer survival of plasma cells. Some other mechanisms like interaction with bone marrow environment and osteoclasts have been described [29].

The first-in-class antibody drug conjugate approved by FDA and EMA for MM patients is belantamab mafodotin (GSK28579176). It is an anti-BCMA ADC composed of humanized IgG1 anti-BCMA MoAb conjugated via a noncleavable linker with monomethyl auristatin F (better known as mafodotin). Mafodotin is a potent microtubule inhibitor (blocks tubulin polymerization). Once the drug is internalized and mafodotin is released, it arrests cell cycle in G2/M phase. Its Fc fragment is defucosylated and facilitates other effects typical for MoAbs such as ADCC and ADCP. This also allows to target and kill nondividing MM cells [30]. Belantamab mafodotin was first evaluated in the phase I dose escalation and expansion trial DREAMM-1. This study enrolled 73 heavily pretreated patients with median five prior lines of therapy including 31 (89%) double refractory patients and 13 (37%) patients refractory to daratumumab. Overall response rate was 60%. Two patients reached stringent CR and three additional patients reached CR. The median PFS was 12 months (follow-up 26.5 moths) [31]. Even though the therapy is targeted, off-target effects of ADC administration do occur. The most frequent adverse events are thrombocytopenia reported in 63% of patients and ocular complications (discussed in detail at the end of paragraph) [32]. The ocular, or more specifically corneal events, are experienced in other clinical trials with mafodotin which is likely to be the responsible agent. This study was followed by the DREAMM-2 trial, which led to registration of belantamab mafodotin. This was a two-arm phase II trial. Overall, 95 patients were recruited into the 2.5 mg/kg group and 99 patients into the 3.4 mg/kg group. The drug was administered intravenously every 3 weeks as monotherapy. Patients were heavily pretreated with median seven lines of prior therapy in the 2.5 mg/kg arm and six lines in the 3.4 mg/kg arm. All patients were pretreated with lenalidomide, 98% with bortezomib, 98% with daratumumab. Almost 90% of patients were refractory to lenalidomide (both groups) and 100% to daratumumab in the 2.5 mg/kg arm and 92% in the 3.4 mg/kg arm. Median PFS was 2.9 months in the 2.5 mg/kg arm and 4.9 months in the 3.4 mg/kg arm. A

VGPR or better was achieved in 18 (19%) in the 2.5 mg/kg arm and in 20 (20%) of 99 patients in the 3.4 mg/kg arm [33]. The most common toxicities were thrombocytopenia, keratopathy, and IRRs. No grade 4-5 IRRs were observed and overall, 17 patients (18%) experienced grade 1-2 IRR and three patients (3%) grade 3 in the 2.5 mg/kg arm. In total, 15 patients (15%) experienced grade 1-2 IRR and one patient (1%) grade 3 in the 3.4 mg/kg arm. Thrombocytopenia was reported in 33 patients (34%) in the 2.5 mg/kg arm and in 58 patients (59%) in the 3.4 mg/kg arm. Grade 4 thrombocytopenia was reported in 11 (12%) patients in the 2.5 mg/kg arm and in 22 (22%) in the 3.4 mg/kg arm. One patient death was attributed to thrombocytopenia in the 3.4 mg/kg arm [33]. The major concern regarding toxicity of belantamab mafodotin is keratopathy. It is clinically characterized by corneal epithelium changes that lead to blurry vision and dry eye [34]. Transient loss of vision is also possible. Keratopathy was very common; grade 1-2 was seen in 41 patients (43%), grade 3 in 26 patients (27%) in 2.5 mg/kg arm. Even higher rates of keratopathy were observed in the 3.4 mg/kg arm: grade 1-2 in 53 patients (54%), grade 3 in 20 patients (20%) and grade 4 in one patient (1%). Keratopathy was also the main reason for treatment delays and dose reductions (22 patients in the 2.5 mg/kg arm and 27 patients in the 3.4 mg/kg arm) and subsequent discontinuation (one patient in the 2.5 mg/kg arm and three patients in the 3.4 mg/kg arm) [33]. All events were reversible with no permanent loss of vision reported [35]. Prophylactic use of corticosteroid eye drops seems to be ineffective in preventing these events. Dose reduction or dose delays are recommended once corneal events occur. Prophylactic measures include preservative-free artificial tears (4-8 times daily) and eventually cooling eye mask in the first hour of administration of belantamab mafodotin and up to 4 h or as tolerated [33].

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