

Belantamab Mafodotin and Multiple Myeloma

Subjects: **Oncology**

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Multiple myeloma (MM) is a hematologic malignancy characterized by excessive clonal proliferation of plasma cells. The treatment of multiple myeloma presents a variety of unique challenges due to the complex molecular pathophysiology and incurable status of the disease at this time. Given that MM is the second most common blood cancer with a characteristic and unavoidable relapse/refractory state during the course of the disease, the development of new therapeutic modalities is crucial. Belantamab mafodotin (belamaf, GSK2857916) is a first-in-class therapeutic, indicated for patients who have previously attempted four other treatments, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. In November 2017, the FDA designated belamaf as a breakthrough therapy for heavily pretreated patients with relapsed/refractory multiple myeloma. In August 2020, the FDA granted accelerated approval as a monotherapy for relapsed or treatment-refractory multiple myeloma. The drug was also approved in the EU for this indication in late August 2020. Of note, belamaf is associated with the following adverse events: decreased platelets, corneal disease, decreased or blurred vision, anemia, infusion-related reactions, pyrexia, and fetal risk, among others. Further studies are necessary to evaluate efficacy in comparison to other standard treatment modalities and as future drugs in this class are developed

belantamab mafodotin

multiple myeloma

1. Current Treatment of Multiple Myeloma

1.1. Overview

Treatment modalities have improved concomitantly with the progression in understanding of the molecular pathogenesis of MM over the past twenty years^[1]. The use of corticosteroids (prednisone and dexamethasone) and alkylating agents (mainly melphalan and cyclophosphamide) as standard therapies began in the mid-1960's. Since the 1990's, treatment protocols have included autologous stem cell transplant (ASCT) for eligible patients ^[1]. Drug classes, including immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and monoclonal antibodies (mAbs), have become the cornerstone of modern multiple myeloma therapy ^{[1][2]}. Combinations of these drug classes have become a standard of care in newly diagnosed transplant-eligible or -ineligible patients, and are utilized in triplet or quadruplet regimens relative to each patient's unique clinical profile^[3].

Despite these advances, a definitive cure for this disease remains elusive; relapse is inevitable, and refractory disease requiring salvage therapy remains a considerable challenge^{[2][24][25][26]}. This has prompted the development of new biologic agents and immunotherapy in the past decade ^{[21][26][27][28]}. The optimal sequence

and combination of novel immunotherapeutic strategies remains to be determined. Current treatment options continue to evolve as we increase our understanding of multiple myeloma's complex molecular pathophysiology and resulting clinical implications ([Table 1](#)).

Table 1. Current Therapeutic Considerations for Multiple Myeloma.

Strategy	Name of the Drug	Mechanism of Action	References
Corticosteroids	Prednisone	Anti-inflammatory and anti-proliferative effects on myeloma cells	[29]
	Dexamethasone		
Conventional Chemotherapy	Cyclophosphamide	Alkylating agent	[30]
	Doxorubicin	Inhibits topoisomerase II; Intercalates into DNA	[31]
	Melphalan	Alkylating agent	[32] [33]
	Bendamustine	Alkylating agent	[34] [35]
Immunomodulatory Drugs (IMiDs)		All: Inhibit production of TNF- α , IL-6, IL-8, VEGF; activate caspase-8	
	Thalidomide		[36]
	Lenalidomide	IL-6 inhibition; caspase-8 activation	[36]
	Pomalidomide	Inhibits Akt phosphorylation; co-stimulates CD28	[37] [38]
	Avadomide (CC-122) *	Co-stimulates CD28	[39]
	Iberdomide (CC-220) *	Cereblon E3 ligase modulator	[39]
Proteasome Inhibitors (PIs)	Bortezomib	Reversibly binds to CT-L/LMP7 subunit; binds C-L /LMP2 and T-L subunits with lower affinity	[40]
	Carfilzomib		[41]
	Ixazomib	Irreversibly binds to CT-L/LMP2 subunit; binds C-L/LMP2 and T-L subunits at high doses	[42]
	Oprozomib *	Binds to beta 5 subunit of 20s proteasome	[43]
	Marizomib *	Irreversibly binds to CT-L /LMP7 subunit	[43]
	Delanzomib *	Binds CT-L/LMP7 and T-L subunits with	[43]

Strategy	Name of the Drug	Mechanism of Action	References
		high affinity; binds C-L/LMP2 subunit with lower affinity Reversibly inhibits CT-L/LMP7 and C-L/LMP2 subunits	
Histone Deacetylase (HDAC) Inhibitors	Panobinostat Romidepsin Ricolinostat Citarinostat *	Pan-Histone Deacetylase Inhibitor Histone Deacetylase Inhibitor Histone Deacetylase 6 Inhibitor Histone Deacetylase 6 Inhibitor	[44][45][46][47] [48]
Monoclonal Antibodies (mABs)	Daratumumab Elotuzumab Denosumab Siltuximab Felzartamab (MOR202) * Isatuximab TAK-079 *	Anti-CD38 Anti CS1/SLAMF7 Anti-RANKL Anti-IL6 Anti-CD38 Anti-CD38 Anti-CD38	[49][50][51][52] [53][54][55]
Immunotherapies	Durvalumab Pembrolizumab Nivolumab Nelfinavir BiTE * CAR-T *	Anti-PDL1 Anti-PD1 Anti-PDL1 Protease Inhibitor Anti-BCMA Anti-BCMA	[59][60][55][56] [57][58]
Novel Agents	Filanesib * Venetoclax * Selinexor	Kinesin Spindle Protein (EG5/KIF11) Inhibitor Selective Inhibitor of BCL-2 Inhibitor of XPO1-mediated nuclear export protein	[61][62][63][64]
Antibody-Drug Conjugates (ADCs)	Belantamab mafodotin Lorvotuzumab mertansine * Milatuzumab doxorubicin * Indatuximab ravtansine *	Anti-BCMA Anti-CD56 Anti-CD74 Anti-CD138	[65][66][67][68]

In 2015, the FDA approved two mAbs, daratumumab and elotuzumab, which selectively target MM cell glycoproteins CD38 and SLAMF7, respectively [1][69]. Several novel immunotherapeutic approaches have emerged since this time. New therapies can target plasma cell-specific antigens to offer an innovative approach to treatment optimization and options for relapsed/refractory disease [21,22]. B-cell maturation antigen (BCMA), a soluble transmembrane glycoprotein overexpressed in MM cells, represents an important target for novel therapeutics. These modalities include antibody-drug conjugates (ADCs) (belantamab mafodotin), bispecific T-cell engagers (BiTEs) (AMG 420), and CAR T-Cell Therapies [1][70].

1.2.1. Anti-BCMA Antibody-Drug Conjugates (ADCs)

Antibody-drug conjugates act as a carrier to deliver cytotoxic agents into MM cells, leading to targeted tumor cell lysis with reduced toxicity in non-targeted tissues. They are composed of a mAb, a linker connecting the drug to the antibody, and the cytotoxic drug. Similar to belamaf, a first-in-class anti-BCMA ADC, there are several emerging anti-BCMA therapeutics currently under development for use in multiple myeloma.

AMG 224 is a compound consisting of an anti-BCMA IgG1 antibody conjugated via a linker (4-[N-maleimidomethyl] cyclohexane-1-carboxylate) to mertansine, an anti-tubulin inhibitor [71]. There is an ongoing phase I study of AMG 224 as monotherapy in heavily pre-treated patients with relapsed or refractory multiple myeloma (NCT02561962). Similarly, MEDI2228 is an ADC using tesirine, a pyrrolobenzodiazepine dimer, as a toxic payload to MM cells. Tesirine is a DNA cross-linking agent with site-specific conjugation to BCMA-Ab1 via a valine-alanine dipeptide linker. MEDI2228 is internalized and trafficked to the lysosome where tesirine is released, resulting in DNA damage, myeloma cell and myeloma progenitor cell death [72]. Current clinical testing is ongoing for its use in the treatment of RRMM (NCT03489525).

HDP-101 is a compound in a new class of ADCs called antibody-targeted amanitin conjugates (ATAC). Amanitin, a toxin contained in the *Amanita phalloides* death cap mushroom, selectively binds to and inhibits the RNA polymerase II subunit A with high affinity. This results in a >1000-fold decrease in transcription and protein synthesis, leading to cell apoptosis and death. Of note, HDP-101 utilizes chemically synthesized amanitin as its toxic payload conjugated to the anti-BCMA mAb via a cathepsin B protease linker [73][74]. A Phase Ia/Ib dose escalation and expansion study is expected to begin in early 2021 to evaluate the effect of HDP-101 in patients with RRMM.

Other anti-BCMA ADCs currently in phase I trials for patients with RRMM include CC-99712 (NCT04036461) and SEA-BCMA, a naked anti-BCMA mAb without conjugate (NCT03582033).

1.2.2. Anti-BCMA Bi-Specific Antibodies (BiAbs)

Bi-specific antibodies are a novel potential therapy for patients with multiple myeloma. Bi-specific T-cell engaging antibody (BiTEs) are a specific type of BiAb that transiently connect immune and tumor cells through their interaction with both CD3 on the T-cell and tumor antigens on the surface of target tumor cells. The molecules are designed with two domains, one that binds CD3 in the T-cell receptor (TCR) complex and the other that recognizes BCMA on MM cells. The binding of CD3 leads to activation of cytotoxic T-cells which release perforin and granzymes to lyse the targeted tumor cells, and interferon- γ which activates macrophages and immune cells [76][75].

Several anti-BCMA BiAbs are in ongoing clinical trials for patients with MM. These include AMG 420 (NCT03836053), AMG 701 (NCT03287908), CC-93269 (NCT03486067), Teclistamab (NCT04557098, NCT03145181, NCT04586426, NCT04108195), TNB-383B (NCT03933735), PF-06863135 (NCT03269136, NCT04649359), REGN5458 (NCT03761108) and REGN5459 (NCT04083534).

1.3. Novel Agents

Novel agents have further expanded the available therapeutic options for patients with relapsed/refractory MM. Selinexor is a first-in-class Exportin-1 (XPO-1) inhibitor, granted accelerated approval in July 2019 for patients with penta-refractory multiple myeloma. Other therapeutics in this class include Filanesib (ARRY-520) and Venetoclax (ABT-199), a kinesin spindle protein inhibitor (KSP) and selective BCL-2 inhibitor, respectively. Filanesib is the only KSP inhibitor that has shown anti-tumor activity in clinical trials. It has demonstrated clinical efficacy in heavily pretreated multiple myeloma patients and may be useful in combination with standard MM backbones, such as PIs and IMiDs [61][62]. Both Filanesib and Venetoclax are under clinical investigation for extended indications, alone and in combination regimens in patients with multiple myeloma.

Immunotherapy via adoptive cell transfer (ACT) is also a promising investigational MM treatment. Current trials are exploring the use of autologous chimeric antigen receptor (CAR)-transduced T-cells, in which host T-cells are engineered with viral vector recombinant DNA techniques. CAR T-cells are then used to initiate a targeted immune response against antigens specific to MM cells[4][26][77].

1.4. Hematopoietic Stem Cell Transplant Eligibility

Given the recent expansion in therapeutic options, individualized treatment for MM is ever evolving and guided by a variety of clinical parameters [24][27]. At this time, eligibility for ASCT and risk-stratification are predominant determinants of the treatment course of newly diagnosed MM[18][3]. ASCT remains the standard for first-line treatment of newly diagnosed MM; therefore, phases of management are generally defined, relative to transplant eligibility[24][78]. Various applications of the aforementioned treatments are utilized, depending on a patient's transplant status. Transplant eligibility is primarily determined by age and existing comorbidities, since these factors predispose patients to toxicity and influence a patient's ability to endure treatment[24][79]. The majority of randomized trials limit ASCT to patients ≤ 65 years of age without significant comorbidities, although consensus regarding an age cutoff has not been established, and practice varies across institutions [79]. Contraindications for ASCT include significant cardiac or pulmonary disorders [24]. Transplant-eligible patients typically undergo 3–4 cycles of the current standard induction therapy, which is a triplet regimen consisting of bortezomib, lenalidomide, and dexamethasone (VRd). Transplant-ineligible patients undergo 8–12 cycles of VRd induction therapy [3][79][80]. Patients undergoing ASCT are treated with cytokines or chemotherapy, after which hematopoietic stem cells are mobilized into peripheral blood and harvested by apheresis[81]. The stem cells can then be used for marrow reconstitution following high-dose chemotherapy. The standard maintenance therapy for both transplant ineligible patients and eligible patients following ASCT is lenalidomide[18].

2. Belantamab Mafodotin Drug Info

In August 2020, the FDA granted accelerated approval to belantamab mafodotin-blmf (belamaf) as a monotherapy treatment for relapsed or treatment-refractory multiple myeloma. Belamaf is a first-in-class biologic for patients who have previously attempted four other treatments, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent[82][83]. As the first approved anti-B cell maturation antigen (BCMA), the use of belamaf may have a large impact on improving progression-free survival in patients with multiple myeloma

who have limited remaining treatment options. BCMA is a cell surface receptor required for the survival of plasma cells. The expression of BCMA can be detected on all CD138+ myeloma cells, but it is not expressed in any other tissues. This receptor specificity allows belamaf to target only the malignant MM plasma cells^{[10][84]}.

Belantamab mafodotin is associated with a high incidence ($\geq 20\%$) of keratopathy^[85]. To mitigate such risks, an ophthalmic exam is recommended prior to and during belamaf therapy in order to assess baseline vision and possible adverse eye effects. Dosage can be reduced or held if ocular toxicity such as blurry vision, dry eyes, or corneal ulcers occurs. Belamaf should be discontinued if ocular toxicity is severe^[82]. Other less common adverse effects, such as thrombocytopenia, infusion-related reactions, pyrexia, fatigue, nausea, constipation, diarrhea, arthralgia, back pain, decreased appetite, and upper respiratory infection, have been reported^[86]. The most common grade 3 or 4 laboratory abnormalities ($\geq 5\%$) include decreases in neutrophils, lymphocytes, platelets, and hemoglobin, along with increases in gamma-glutamyl transferase and creatinine^[82].

There is a paucity of data on the use of belantamab during pregnancy and breastfeeding. Because belantamab is a large protein molecule, the amount excreted in breastmilk is postulated to be very low. However, belantamab is conjugated with mafodotin, a small-molecule toxin, which may be excreted into milk. As such, it is recommended that patients use effective contraception and avoid breastfeeding while taking the medication and for 3 months after the last dose^[87].

3. Belantamab Mafodotin Mechanism of Action

3.1. Antibody Drug Conjugate (ADC)

Belantamab mafodotin (Blenrep, GSK2857916 or J6M0-MMAF) is an antibody-drug conjugate (ADC) that demonstrates a multifaceted mechanism of action based on three main components. ADCs are a new class of cancer therapeutics that confer unique pharmacologic activity via mAbs covalently conjugated to a cytotoxic agent via a specialized linker^[28]. The mAb component of an ADC selectively targets tumor cells and elicits a host immune response, while simultaneously delivering a cytotoxic payload to the cell^{[25][86]}. Belamaf consists of a humanized, afucosylated IgG1 mAb conjugated to monomethyl auristatin-F (MMAF) via a protease-resistant maleimidocaproyl linker^{[25][70]}.

3.2. Target Antigen-B-Cell Maturation Antigen (BCMA)

The high specificity of belamaf for MM cells is a hallmark feature derived from the mAb component, which targets B-Cell Maturation Antigen (BCMA). BCMA, a member of the tumor necrosis factor receptor superfamily, is a notable tumor-associated antigen of particular interest due to almost exclusive BCMA expression on mature B-cells and plasma cells. BCMA is integral to plasma cell maturation and differentiation. BCMA is also overexpressed during the malignant transformation of plasma cells, making it an ideal pharmacologic target in the treatment of MM^{[21][25][70]}. B-cell activating factor (BAFF) and APRIL (a proliferation-inducing ligand) are high-affinity ligands for BCMA that promote proliferation and viability of MM cells in the bone marrow. BAFF is a BCMA agonist that

induces differentiation, proliferation, and antibody production [21][70]. The binding of belantamab to BCMA receptors impedes the pro-survival cytokine-signaling effects of BAFF and APRIL on malignant plasma cells [21][28].

3.3. Afucosylated Monoclonal IgG1 Antibody

Belamaf induces enhanced tumor cell lysis via natural killer cell-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) [28][70][86]. While naturally occurring IgG antibodies exhibit significant core-fucosylation on the N-glycan of the Fc region, the IgG1 mAb in belantamab mafodotin is afucosylated. The removal of these fucosyl groups enhances IgG1 Fc binding affinity to FcγRIIIa (CD16) on natural killer cells, which is a well-known strategy for augmenting effector cell ADCC of cancer cells [21][25].

3.4. Monomethyl Auristatin-F (MMAF) and Linker

After belamaf binds, the mAb drug complex is internalized, allowing MMAF to induce apoptosis [82]. MMAF inhibits tubulin polymerization to disrupt microtubules and arrest myeloma cells at the G2/M checkpoint [21]. Of note, the protease-resistant properties of the linker used in belamaf requires I

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