Brief Insight About B-cell Maturation Antigen (BCMA) in Multiple Myeloma

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Abstract

Background: There have been significant advancements in the treatment of multiple myeloma (MM) in the previous decade, yet a large percentage of patients still do not react or have a short duration of response to existing medications. In addition, not all patients will have the same level of tolerance for these treatments, and they might cause significant morbidity. Relapsed or refractory MM develops when individuals develop resistance to treatments for multiple myeloma, which is a condition for which there is now no cure. Consequently, there is a need for MM medicines that have not yet been developed, ideally ones that have new action mechanisms that can produce long-lasting effects, avoid drug resistance, and/or have better side effects. B-cell maturation antigen (BCMA) is an antigen that mature B cells preferentially express. It has been linked to multiple myeloma (MM) in both humans and preclinical animals, suggesting that it could be a useful treatment target for MM. Further evidence for BCMA's utility as an MM biomarker comes from its association with clinical state, its predictive significance, and its applicability to patient populations that have historically been challenging to monitor. Here, we take a look at three typical approaches to treating MM that target BCMA: chimeric antigen receptor (CAR)-modified T-cell therapy, antibody-drug conjugates, and bispecific antibody complexes. We summarise early clinical results from studies utilising these treatments, which include the immuno-oncology treatment AMG 420 (BiTE®, "bispecific T-cell engager"), the antibody-drug combination GSK2857916, and other CAR T-cell therapeutic agents such as bb2121, NIH CAR-BCMA, and LCAR-B38M. The minimal residual disease negativity rates are high, and several of these treatments have shown notable antimyeloma activity. The promise of BCMA-targeted treatments for MM is highlighted by these clinical data. Importantly, preliminary clinical data indicate that these treatments have the potential to provide deep and long-lasting effects, which bodes well for future research into early therapy modalities, such as those for newly diagnosed MM.

Keywords: B-cell Maturation Antigen, Multiple Myeloma

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Introduction

Multiple myeloma (MM) accounts for ~10% of all hematologic malignancies in the United States, with the highest incidences being observed in developed countries [1]. Considerable advances have been made in the last decade regarding the knowledge of the underlying biology and natural progression of MM. In addition, the use of proteasome inhibitors and immunomodulatory imide drugs (IMiDs) has improved treatment options for this condition [1]. Despite these advances, the 5-year survival rate for patients with MM is ~50% and can be lower in high-risk patients (e.g., frail elderly patients, MM with high-risk cytogenetics), highlighting an unmet need for improved treatment options for MM [1, 2]. With current approaches, MM is not considered curable and relapse is considered an inevitable part of the disease course, leading to the development of relapsed/refractory MM (RRMM) [1, 3,4,5]. Patients with RRMM have progressively shorter durations of remission and lesser responses to standard salvage therapies after relapse and treatment resistance. Of note, patients who progress within 18 months of starting initial therapy have particularly poor outcomes [1]. Ultimately, there remains an unmet need for novel therapies for newly diagnosed MM that could provide more durable responses than standard therapies, or even potentially a cure if used early in the disease course, as well as therapies for RRMM that can evade resistance to other therapies [1, 3, 4].

B-cell maturation antigen (BCMA) has emerged as a promising target for MM therapies. Currently, the three most common treatment modalities for targeting BCMA are bispecific antibody constructs including BiTE® (bispecific T-cell engager) immuno-oncology therapies, antibody–drug conjugates (ADCs), and chimeric antigen receptor (CAR)-modified T-cell therapy. In this review, we provide an overview of therapies from these classes that have presented or published clinical data, including the BiTE® molecule AMG 420, the ADC GSK2857916, and several CAR T-cell therapies including NIH CAR-BCMA, bb2121, and LCAR-B38M.

Materials and methods

Published or presented clinical data for BCMA-targeted therapies were identified through PubMed (December 2, 2013 through May 16, 2019) and via search of abstracts from major oncology and hematology conferences (2016 through May 2019, up to and including ASCO 2019). BCMA-targeted therapies with clinical data presented or published as of May 16, 2019 are summarized in this review. The search terms used were “BCMA”, “CD269,” and “TNFRSF17” for the therapeutic target and “MM” and “myeloma” for the disease state. Major oncology and hematology conferences included American Society of Hematology, American Society of Clinical Oncology (ASCO), American Association for Cancer Research, European Hematology Association, International Myeloma Workshops, and Transplantation & Cellular Therapy Meetings

(cosponsored by the American Society for Transplantation and Cellular Therapy and the Center for International Blood & Marrow Transplant Research). The most recent evidence regarding the biology of BCMA and its use as a biomarker was assessed using published research data and review articles.

Rationale for targeting BCMA for treatment of MM

Biology of BCMA

B-cell maturation antigen, also referred to as TNFRSF17 or CD269, is a member of the tumor necrosis factor receptor (TNFR) superfamily [6, 7]. Ligands for BCMA include B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), of which APRIL has a higher affinity for BCMA [8]. BCMA is expressed preferentially by mature B lymphocytes, with minimal expression in hematopoietic stem cells or nonhematopoietic tissue, and is essential for the survival of long-lived bone marrow plasma cells (PCs), but not overall B-cell homeostasis [9,10,11,12]. Membrane-bound BCMA can undergo γ-secretase–mediated shedding from the cell surface, leading to circulation of soluble BCMA (sBCMA) and reduced activation of surface BCMA by APRIL and BAFF [7, 13, 14].

Biology of BCMA in MM

The overexpression and activation of BCMA are associated with progression of MM in preclinical models and humans, which makes it an attractive therapeutic target [7, 15, 16]. Murine xenografts with induced BCMA overexpression grow faster than BCMA-negative controls. This overexpression leads to the upregulation of canonical and noncanonical nuclear factor kappa-B pathways, as well as enhanced expression of genes critical for survival, growth, adhesion, osteoclast activation, angiogenesis, metastasis, and immunosuppression [15]. Similar results are observed after APRIL-induced activation of BCMA in ex vivo human MM cells [15]. Furthermore, sBCMA can inhibit the activity of BAFF via complex formation, leading to MM-associated immunodeficiency [16]. BCMA is also expressed at much lower concentrations (9- to 50-fold lower) by plasmacytoid dendritic cells, which are known to help promote MM PC survival in the bone marrow environment [13, 17]. Additional details regarding the role of BCMA in B-cell biology and in MM, including illustrations, can be found in other reviews [18,19,20,21].

BCMA as a biomarker for diagnosis of MM

Malignant MM PCs typically compose a small subset of bone marrow cells, so accurate identification of these cells is important to ensure representative characterization of the disease [22]. The traditional MM biomarker CD138 is highly specific to PCs but rapidly disappears from the cell surface when sample analysis is delayed or if the sample is frozen [22]. Therefore, additional biomarkers to diagnose or monitor MM are needed.

BCMA is highly expressed on malignant PCs collected from patients with MM compared with normal bone marrow mononuclear cells (BMMCs) from healthy donors, and several studies have assessed whether BCMA has value as a marker for diagnosis, prognosis, and/or as a predictor of treatment response [7, 23,24,25,26,27,28]. In contrast with CD138, BCMA is readily identified in delayed and frozen MM samples [22]. The levels of membrane-bound BCMA can be measured by various techniques (e.g., flow cytometry, immunohistochemistry), with flow cytometry being more sensitive than immunohistochemistry, though the quantification of BCMA levels can differ between studies owing to differences in methodology [7, 23, 28]. Interestingly, BCMA mRNA is expressed at similar levels by malignant PCs in patients with newly diagnosed MM and RRMM, suggesting that BCMA may be a promising therapeutic target throughout the MM disease course [24].

sBCMA levels are elevated in patients with MM and correlate with the proportion of MM cells in BMMC samples [7]. sBCMA may also serve as a valuable biomarker in select patient populations that are otherwise difficult to monitor. The levels of sBCMA are independent of renal function, which permits its use as a biomarker in patients with renal insufficiency, and sBCMA is detectable in the serum of patients with nonsecretory disease as well as in nonsecretory murine xenograft models [7, 21, 29].

BCMA as a tool for prognosis and treatment response

The clinical course of MM is variable and there remains a need for reliable methods to assess the prognosis of patients and monitor their disease status [29]. The levels of sBCMA have prognostic value, as patients with higher levels, particularly those ~25–325 ng/mL or higher, have poorer clinical outcomes than those with lower sBCMA values [7, 25, 29]. Similarly, baseline sBCMA levels have been suggested to be inversely correlated with future response to treatment [7, 30], though this correlation has not been observed in all studies [25, 31,32,33,34]. Higher sBCMA levels in patients with monoclonal gammopathy of undetermined significance or smoldering MM also appear to be associated with an increased risk of progression to MM [35].

The measurements of sBCMA may also be useful for monitoring patient response to ongoing therapy. Patients who have responded to therapy have reduced sBCMA levels compared with patients with progressive disease [7, 27]. Changes in sBCMA levels tend to correlate with the clinical status of patients with MM during anti-MM treatment, as well as tumor mass in preclinical models [7, 21, 26,27,28,29, 36, 37]. For example, one study found that patients with a complete response (CR) had lower sBCMA levels (median, 38.9 ng/mL) than patients with a partial or minimal response (median, 99.7 ng/mL) or nonresponsive disease (median, 195.3 ng/mL) [29]. Because sBCMA has a much shorter serum half-life (24–36 h) compared with M-protein (3–4 weeks), changes in sBCMA more rapidly reflect changes in disease status than M-protein levels and therefore may serve as a useful alternative and potentially more sensitive marker for monitoring

disease status [20, 34]. Notably, sBCMA levels do not appear to change more significantly in response to one particular class of anti-MM therapy over others [7].

The efficacy and durability of anti-BCMA therapies may be particularly dependent on sBCMA levels. It has been demonstrated that sBCMA can bind to and interfere with anti-BCMA antibodies [38]. In this case, drugs that inhibit γ-secretase could enhance the efficacy of BCMA-targeted therapy by reducing shedding of BCMA from the cell surface and subsequent interference of BCMA-targeted therapies by sBCMA [20, 21, 38]. An additional approach could be to use anti-BCMA monoclonal antibodies (mAbs) with higher specificity for membrane-bound BCMA than sBCMA [39]. As it is currently unclear whether changes in membrane-bound or sBCMA levels during therapy could alter the long-term efficacy of anti-BCMA therapies, additional investigation into the relationship between baseline sBCMA and response to BCMA-directed therapies is warranted.

Treatment modalities to target BCMA

Given the selective expression of BCMA on malignant PCs, several BCMA-targeted therapies have been developed with the aim of eradicating these malignant cells through distinct mechanisms. Current anti-BCMA therapies generally fall into one of three classes: bispecific antibody constructs, including BiTE® (bispecific T-cell engager) molecules, ADCs, and CAR T-cell therapy. In this section, we provide an overview of anti-BCMA therapies in these classes, focused on therapies with clinical data.

Use of minimal residual disease measures in MM

In addition to impressive response rates by International Myeloma Working Group criteria, several BCMA-targeted therapies described below have demonstrated minimal residual disease (MRD)-negative status in heavily pretreated patients with RRMM [27, 34, 40, 41]. Minimal residual disease is defined as the presence of a small number of tumor cells after treatment that is below the level of detection using conventional morphologic assessments (e.g., stringent CR [sCR], CR). The precise definition of MRD negativity depends on the threshold and detection method used (e.g., flow cytometry, next-generation sequencing) [42, 43]. The use of MRD endpoints in clinical studies of hematologic malignancies has been increasing over time, and achieving MRD negativity is associated with better clinical outcomes [42, 44]. Even in cases in which patients achieve a CR by conventional measurements, patients who are MRD negative may have longer overall and progression-free survival (PFS) compared with patients who achieve a CR but are MRD positive [42, 43]. Therapies that help patients attain MRD-negative status along with deep morphological remission (i.e., CR) could ultimately lay the groundwork for achieving a cure for MM [42]. However, there are limitations to MRD measurements in the RRMM setting. First, the measurement and definition of MRD may not always be reproducible across studies, as techniques for assessing MRD differ in sensitivity and the cutoff used for defining MRD (e.g., 10^{-4}, 10^{-6}) have not yet been standardized [42, 43]. Second, MRD negativity cannot be directly interpreted as a

cure, and some patients who do not achieve deep molecular remission still achieve long-term disease control [42]. Third, there are limited clinical data that have directly assessed the role of MRD in MM for guiding treatment decisions [42, 43]. Finally, the assessment of MRD in MM to date has been primarily in the newly diagnosed or maintenance setting; therefore, the role of MRD in RRMM prognosis or guidance of future treatment remains unclear [42].

Bispecific antibody constructs

Bispecific antibody constructs are engineered to have dual antigen specificity to facilitate cell-to-cell interactions between the patients' own T cells and malignant cells expressing tumor-specific antigens [45]. Several different structures have been used for bispecific antibody constructs investigated in oncological clinical trials, as illustrated in a recent review [46]. Forms of these constructs that have been investigated in MM include BiTE® (bispecific T-cell engager; Amgen, Thousand Oaks, CA, USA) molecules and DuoBody® (Genmab A/S, Copenhagen, Denmark) technology, among others. BiTE® molecules are fusion proteins consisting of single-chain variable fragments (scFv) with unique antigen specificities [45]. DuoBody® bispecific antibody constructs are generated via Fab-arm exchange, which uses mutations and recombination at the CH3–CH3 antibody interface to combine heavy and light chain homodimers from two separate mAbs into a single heterodimeric, bispecific antibody structure [47].

Of these two modalities, BiTE® molecules are currently the only type of bispecific antibody construct with preliminary efficacy data from clinical trials in MM [41, 48]. The rationale for use of BiTE® molecules in MM is also supported by the antitumor activity of blinatumomab, which is approved for treatment of select patients with acute lymphoblastic leukemia (ALL). Blinatumomab is a BiTE® molecule that engages $CD3^+$ cytotoxic T cells and $CD19^+$ B cells to recognize and eliminate $CD19^+$ ALL blasts, leading to a survival benefit of 3.7 months compared with chemotherapy in patients with Philadelphia chromosome-negative B-cell ALL [49, 50]. BiTE® molecules for MM incorporate one scFv that engages the T-cell receptor CD3ε subunit, while the other engages a tumor-specific antigen expressed on malignant cells. This dual engagement leads to the formation of a cytolytic synapse between the T cell and the BCMA-expressing cell. Because formation of the cytolytic synapse is independent of standard antigen recognition and costimulation mediated by major histocompatibility complex class I, lysis of the target tumor cell occurs in a manner that is independent of immune escape mechanisms that tumor cells may develop to evade detection. CD3ε is expressed by all $CD8^+$ and $CD4^+$ T cells, which enables polyclonal T-cell activation, expansion, cytokine production, and tumor cell lysis [51].

AMG 420

AMG 420, formerly BI 836909, is a BCMA × CD3 BiTE® molecule that has been investigated in patients with RRMM (Table 2). Data from a first-in-human, phase 1 dose-escalation study (NCT02514239) reported an objective response rate (ORR) of 70% (7/10) at 400 μg/day, which included five MRD-negative CRs (i.e., a 50% MRD-negativity rate), one VGPR, and one PR

[41, 48]. Minimal residual disease in this study was defined as <1 tumor cell per 10^4 normal cells in the bone marrow by flow cytometry. As of cutoff for the most recently presented data, some responses were durable over 1 year, and two patients were in ongoing treatment at the 400 μg/day dose. Overall, median time to any response was 1 month. Serious AEs (SAEs) observed in more than one patient were infections and polyneuropathy (PN). Treatment-related SAEs included two grade 3 PNs and one grade 3 edema. Grade 2 or 3 cytokine release syndrome (CRS) was observed in 3 of 42 patients included in the phase 1 study. AMG 701, a half-life extended BiTE® molecule targeted to BCMA, appears to induce potent T cell-directed lysis of BCMA-positive MM cells in vitro [52] and is in clinical development.

PF-06863135

PF-06863135 (PF-3135) is a humanized bispecific IgG mAb consisting of anti-CD3 and anti-BCMA-targeting arms paired through hinge-mutation technology within an IgG2a backbone [53]. Safety results from a phase 1 dose-escalation study in patients with RRMM suggest that PF-3135 is well tolerated, with no dose-limiting toxicities or CRS events observed in the first five patients treated [53].

Other bispecific antibody constructs in clinical development

Other BCMA-targeted bispecific antibody constructs in clinical development that have demonstrated preclinical efficacy include JNJ-957 (a humanized BCMA × CD3 bispecific antibody construct with DuoBody® technology) [54], REGN5458 (a humanized BCMA × CD3 bispecific antibody construct) [55], TNB-383B (a fully human BCMA × CD3 bispecific antibody construct with a low-activating αCD3 arm that preferentially activates effector T cells over regulatory T cells) [56], and CC-93269 (previously known as BCMA-TCB2/EM901, a dual-arm, human IgG1-based bispecific antibody construct with one CD3 and two BCMA-binding sites) [57, 58].

Antibody–drug conjugates

ADCs are tumor-associated antigen (TAA)-targeted mAbs conjugated to toxic payloads, such as tubulin polymerization inhibitor monomethyl auristatin F (MMAF), pyrrolobenzodiazepine (PBD), or the RNA polymerase II inhibitor α-amanitin, using a cleavable or non-cleavable linker [17, 31, 59, 60]. Once bound to TAA-expressing target cells, ADCs are internalized and the toxic payload is released to induce DNA damage and cell death [17, 39, 59]. Cleavable linkers are enzymatically processed within the target cell, while the action of ADCs with noncleavable linkers requires degradation of the attached antibody within lysosomes to release the payload [59]. Currently, one anti-BCMA ADC (GSK2857916) has demonstrated antimyeloma activity in a phase 1 trial

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