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Role of Bispecific antibody for Multiple Myeloma; A literature Review

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ABSTRACT

Multiple myeloma (MM), as defined by a clonal plasma cell proliferation, manifests as end organ damage caused by the abnormally high monoclonal paraprotein.In this article, we have reviewed the potential benefits of Bispecific antibodies (BsAbs) in MM patients. In addition, new BsAbs developments and clinical trials for various MM targets are discussed in detail. Bispecific antibodies are the types of antibodies that have two different antigen binding sites in one molecule. There are 100 different classes of BsAb and all these can be divided into 2 main categories based on their fragments and both categories are under trials for MM.Despite some studies showing adverse effects development of these new treatments is going to greatly contribute to improve outcomes for a wide group of patients which also requires further clinical studies to be conducted with focus on demonstration of efficacy and safety profile.

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Introduction

Multiple myeloma (MM), as defined by a clonal plasma cell proliferation, manifests as end organ damage caused by the abnormally high monoclonal paraprotein. MM forms a part of the spectrum of monoclonal gammopathy. 1.8% of all new cancer cases in the United Stated are contributed by MM. Geriatric population is the most affected by MM with a median age of diagnosis as 65 years [1]. It is expected that in 20 years the number of cases diagnosed annually will almost double. It is twice as common in African Americans than Caucasians and male-to-female ratio is 3 to 2 [2]. The survival outlook for multiple myeloma is changing sequentially as its treatment evolves. Most profound impact has been reported with the use of proteasome inhibitors and immunomodulatory drugs. Recently, monoclonal antibodies have been approved for the treatment of multiple myeloma. Survival has also been reported to improve with the ancillary care for bone disease related to myeloma and other interventions. Median overall survival has improved from one to two years to seven to eight years. Also, the patients experience a better quality of life and long-term survival. Five-year survival has risen to 45% in 2007 which previously used to be 30% in 1990 [3,4]. With the development of these newer therapies, there has been a possibility of deep responses such as minimal residual disease-negative state. More than 12,000 patients die annually out of the 30,000 new cases of MM [5]. The age-adjusted incidence in the United States has remained 4 per 100,000 annually for decades [6].

In order to diagnose there must be ≥10% clonal bone marrow plasma cells or plasmacytoma proven on biopsy with one or more multiple myeloma defining events (MDE) such as CRAB (hypercalcemia, renal failure, anemia, or lytic bone lesions), ≥60% bone marrow clonal plasmacytosis, serum involved/uninvolved free light chain (FLC) ratio ≥100 (provided involved FLC is ≥100 mg/L), or >1 focal lesion on magnetic resonance imaging. The treatment of MM becomes problematic because of this genetic complexity. As yet MM is primarily treated with chemotherapies in combination with proteasome inhibitors, anti-resorptive agents such as bisphosphonates, corticosteroids and bone marrow transplantation.

Bispecific antibodies (BsAbs) offer a promising immunotherapeutic approach for various malignancies including MM.

In this article, we review the potential benefits of BsAbs in MM patients. In addition, new BsAbs developments and clinical trials for various MM targets are discussed in detail. Finally, we discuss the use of BsAbs as the future treatment of MM as well as the obstacles that need to be overcome.

What are Bispecific Antibodies

Bispecific antibodies-are types of antibodies that have two different antigen binding sites in one molecule. With the help of hybridoma technology first monoclonal BsAbs were produced in the 1980s. Although it was first described in the 1960s, the first article mentioning its therapeutic use was published in 1992. Due to its therapeutic use, it has gained interest in the scientific community and no publications on this topic have increased significantly. Monoclonal antibodies are derived from a one parent cell which are identical immune cells. They bind to the same epitope which is Abs' binding site on the antigen. We are focusing on the development of Abs that can not only bind two or more antigens but also conjugate to chemo and radiotherapy agents.

BsAbs are being developed that has 2 antigen binding sites in which one binds to CD3 receptor that is responsible for activating cytotoxic T lymphocytes and other site binds to antigen specific to tumor cells e.g., CD19, CD20, Epithelial cell adhesion molecules [EpCAM], CEA etc [7]. Thus, BsAbs help activate cytotoxic T lymphocytes against the antigen specific to tumor cells and promotes the destruction of tumor cells. These antibodies are not only directed against the tumor cells but are also being studied for the treatment of other diseases.

Advantages of Bispecific Antibodies

In contrast to monospecific antibodies, bio specific antibodies have several advantages.

1. BsAbs have greater binding specificity compared to monospecific antibodies because they interact with two different surface antigens.
2. They are responsible for activating specific effector cells of the immune system like cytotoxic T cells which helps in more robust killing of the target.
3. They can also be conjugated to chemo-radio agents.
4. They are cheaper compared to two monospecific drugs used for the treatment of one disease.
5. Importantly, modulator of one disease may play an important role in modulation/co-expression of receptors involved in other diseases, thus targeting two different growth promoting receptors on a single tumor not only increases the antitumor effect of the drug but also suppresses the development of the resistance [8,9].

These antibodies are being studied as potential treatments for different diseases including cancer, autoimmune diseases, bleeding disorders, chronic inflammatory diseases and infections.

T cells are key mediators of the adaptive immune system which enhance the destruction of cancerous cells via different mechanisms [10]. These mechanisms include; recognizing and attacking infected host cells, increasing the production of cytokines and regulating the immune response. Due to these factors T cells are being considered for the treatment of patients suffering from MM. In 2009, European Union clinically approved Catumaxomab (anti-EpCAM × anti-CD3), the first BsAb. This was followed by approval of BaAb, Blinatumomab (anti-CD19 × anti-CD3) by FDA in 2014 [11-13]. Since then a lot of research and clinical trials have been done on a variety of BsAb. Among these, BsAb-emicizumab has been approved by the FDA for the treatment of hemophilia A [14,15]. However, despite 13 BsAb in clinical trials, no medicine has been approved for the treatment of MM as of now. In 2017, a clinical study was started to observe the effects of BsAb-blinatumomab in relapsed/refractory MM patients.

Types of Bispecific Antibodies

There are 100 different classes of BsAb and all these can be divided into 2 main categories based on their fragments i.e. crystallizable (fc) region and antigen binding (fab) variable region. BsAb under both these categories are under trials for MM. The Fc domain BsAb can be further classified into 2 categories based on the presence and absence of the Fc segment.

The presence of the Fc domain allows BsAb to be more stable, prolonging its half life in vivo [16]. It induces the migration of natural killer cells at the site of tumor cells by activation dependent cell mediated cytotoxicity (AACD). At the same time it stimulates the complement mediated cytotoxicity by fixing the complement. Currently a large number of BsAb are being produced by recombinant DNA technology, although clinical trials were initially run to generate them by chemically combining 2 monoclonal ab.

Among many molecules expressed by MM cells on their surfaces, B-cell Maturation Antigen (BCMA) happens to be the most recognized antigen; clinicals trials directed to generate antibodies against it seem most promising[17,18]. This is due to the fact that BCMA is expressed by the neoplastic cells in large amounts and the only other cells in the body which normally produce it in negligible amounts are pDC [19-21]. Thus making it the best target for any therapeutic measures taken towards MM. So far CAR and ADC happen to be T- cell mediated BCMA directed interventions directed against MM other than BsAb.

Currently, no further studies are evaluating AMG 420 based on the pharmacokinetics mentioned earlier. However, a study evaluating AMG 701, an extended half-life BiTE without the need for continuous infusion, is in progress [22].

A humanized Ig-like BiAb pf-06863135 (PF-3135) is currently undergoing a dose-escalation study in RRMM patients with one infusion weekly, and the results of the first 17 patients have been reported. The clinical benefit rate (defined as best response > stable disease) is 41 %, and dose intensification is still ongoing. One patient showed a minimal response (6%), three patients had G > 3 AEs, and one patient had non-hematologic AE with increased blood liver enzymes (LFT).

Another Ig-like BiAb CC-93269 that asymmetrically targets BCMA via two binding sites and CD3 via one binding site is currently being studied in heavily pre-treated RRMM patients in phase-1 dose-escalation trial with the results of the first 30 patients already been reported. It is given intravenously over 2Hr; weekly in cycles 1-3, on alternative weeks in cycles of 4-6, and every 28 days after that. The ORR was 43% throughout the dose cohort approaching 89%, with the highest tested dose of 10mg; thus, it became dose-dependent. A milder CRS was frequently observed (all grades 77%; G >3 4%), neutropenia (G >3 43% and infections (G>3 30%) being other main toxicities. Thus, Dexamethasone prophylaxis was given to all patients treated with doses > 6mg.

Teclistamab is another Ig-like BiAb, studied in RRMM patients in a phase-1 dose-escalation trial with the results of the first 78 patients already being reported. Priming doses followed by weekly infusions are given at different dose levels (0.3-720 mcg/Kg). The ORR (overall response rate) is 67% in 12 patients treated with the highest dose (270mcg/Kg), while no efficacy data is available for the 720mcg/kg dose cohort. CRS was commonly observed (56%), mostly G1 or 2, and Neurotoxicity was reported in 8% of patients.

Several studies have reported the expression of CD19 by MM stem cells, and clinical studies are in progress to evaluate the antimyeloma activity of Blinatumomab in humans. A phase 1 clinical study (NCT03173430) is in progress to determine the feasibility, safety, and antimyeloma activity of Blinatumomab post-Autologous HSCT. Blinatumomab is administered after high-dose Melphalan and Autologous stem cell transplant.

The patient, a 70-year old female, in partial remission with Lenalidomide therapy for MM, developed pre-B-ALL, underwent cytoreductive treatment, and started on Blinatumomab induction therapy, resulting in complete remission of her ALL and a good partial response to MM as per the International Myeloma Working Group criteria [23]. Although this patient had an atypical MM tumor with CD19 positive staining MM cells, it provides promising results of antimyeloma activity of Blinatumomab [23].

The primary targets for MM are BCMA, Syndecan-1 (CD-138), the target of Wue- 1 mAb, and Fc receptor-like 5 (Fcrl5 or FcHR5) [24-28]. Multiple Myeloma is largely an incurable disease with relapse and development of PI- and or IMiD-resistance. Thus, the management of late-stage relapsed/refractory RRMM, especially, is challenging in clinical practice.The Trials of use of bispecific antibodies in MM are shown in the Table 1.

Table 1: The Trials in literature mentioning the use of bispecific antibodies in multiple myeloma (MM)

Drug name	Targets	Design	Trial type	Study type	Estimated participants	Estimated enrollment	Reference
PF-06863135	BCMA × CD3	IgG2a Fc region	Phase 1	Interventional	81	April 2023	NCT03269136
TNB-383B	BCMA × CD3	IgG4 Fc region	Phase 1	Interventional	133	December2021	NCT03933735
REGN5458	BCMA × CD3	Fc region, Fab arms	Phase 1/2	Interventional	200	December2022	NCT03761108
REGN5459	BCMA × CD3	Fc region, Fab arms	Phase 1/2	Interventional	70	March 2025	NCT04083534
CC-93269	BCMA × CD3	Trivalent, Fc region	Phase 1	Interventional	175	November 2026	NCT03486067
JNJ-64007957	BCMA × CD3	IgG1 Fc region	Phase 1	Interventional	204	September 2024	NCT03145181
AMG420	BCMA × CD3	BiTE	Phase 1	Interventional	43	July 2020	NCT02514239
AMG701	BCMA × CD3	Half-life extended BiTE (scFvs plus Fc region)	Phase 1	Interventional	408	November 2027	NCT03287908
AMG424	CD38 × CD3	Fc region, scFv x Fab arms	Phase 1	Interventional	27	June 2020	NCT03445663
GBR1342	CD38 × CD3	Fc region, scFv x Fab arms	Phase 1	Interventional	197	May 2024	NCT03309111
Blinatumomab	CD19 × CD3	BiTE	Phase 1	Interventional	6	January 2019	NCT03173430
BFCR4350A	FcRL5 × CD3	IgG1Fc region	Phase 1	Interventional	300	August2022	NCT03275103
JNJ-64407564	GPRC5D × CD3	IgG1Fc region	Phase 1	Interventional	245	March 2025	NCT03399799

Limitations

Most of the studies included in our review are either ongoing clinical trials or to be conducted in future and have not arrived at a definite conclusion yet. Also, there were not enough clinical trials to determine the role and efficacy of bispecific antibodies in treatment of multiple myeloma. Our review will hopefully have potential benefits for future researchers for carrying out further studies regarding this topic.

Conclusion

With several benefits of bispecific antibodies compared to other therapies, they are being studied for their use in various diseases like cancer, autoimmune, infectious disease etc. BsAb PF-3135 has shown to be beneficial in an ongoing study with some adverse effects reported in few patients. Other BsAb like CC-93269 acting via BCMA and CD3 antagonism and teclistamab are also being studied. Blinatumab has also shown promising antimyeloma activity. However, the studies on these agents are in initial phases. These agents have exhibited promising efficacy in preclinical and early clinical studies in MM, specifically the anti-BCMA Abs seem to be promising in RRMM [29].

Despite some studies showing adverse effects like CRS and development of HAMA associated with use of BsAb, development of these new treatments is going to greatly contribute to improve outcomes for a wide group of patients which also requires further clinical studies to be conducted with focus on demonstration of efficacy and safety profile.

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References

1. Regelink JC, Minnema MC, Terpos E, Kamphuis MH, Raijmakers PG, et al. (2013) Comparison of modern and conventional imaging techniques in establishing multiple myeloma-related bone disease: a systematic review. British journal of haematology 162: 50-61
2. Mateos MV, Landgren O MGUS (2016) Smoldering Multiple Myeloma: Diagnosis and Epidemiology. Cancer Treat Res 169: 3-12.
3. Bianchi G, Anderson KC (2014) Understanding biology to tackle the disease: multiple myeloma from bench to bedside, and back. CA Cancer J Clin 64: 422-444.
4. SEER stat fact sheets: myeloma. National Institutes of Health (2016) National Cancer Institute Surveillance, Epidemiology, and End Results Program. http://seer.cancer.gov/statfacts/html/mulmy.html.
5. Landgren O, Weiss BM (2009) Patterns of monoclonal gammopathy of undetermined significance and multiple myeloma in various ethnic/racial groups: support for genetic factors in pathogenesis. Leukemia 23: 1691-1697.
6. Spiess C, Zhai Q, Carter PJ (2015) Alternative molecular formats and therapeutic applications for bispecific antibodies. Mol Immunol 67: 95-106.
7. Zhang X, Yang Y, Fan D, Xiong D (2017) The development of bispecific antibodies and their applications in tumor immune escape. Exp Hematol Oncol 6: 12.
8. Kontermann RE (2012) Dual targeting strategies with bispecific antibodies. MAbs 4: 182-197.
9. Fabbri M, Smart C, Pardi R (2003) T lymphocytes. Int. J. Biochem. Cell Biol 35: 1004-1008.
10. Velasquez MP, Bonifant CL, Gottschalk S (2018) Redirecting T cells to hematological malignancies with bispecific antibodies. Blood 131: 30-38.
11. Linke R, Klein A, Seimetz D (2010) Catumaxomab. MAbs 2: 129-36.
12. Approved antibodies The Antibody Society (2019) Available online at: https://www.antibodysociety.org/resources/approved-antibodies/.
13. Franchini M, Marano G, Pati I, Candura F, Profili S, et al. (2019) Emicizumab for the treatment of haemophilia A: a narrative review. Blood Transfus 17: 223-228.
14. Labrijn AF, Janmaat ML, Reichert JM, Parren PWHI (2019) Bispecific antibodies: a mechanistic review of the pipeline. Nat Rev Drug Discov 18: 585-608.
15. Kontermann RE, Brinkmann U (2015) Bispecific antibodies. Drug Discov Today 20: 838-847.
16. Tai YT, Anderson KC B (2019) cell maturation antigen (BCMA)-based immunotherapy for multiple myeloma. Expert Opin. Biol. Ther 19: 1143-1156
17. Shah N, Chari A, Scott E, Mezzi K, Usmani SZ (2020) B-cell maturation antigen (BCMA) in multiple myeloma: Rationale for targeting and current therapeutic approaches. Leukemia 34: 1-21.
18. Tai YT, Mayes PA, Acharya C, Zhong MY, Cea M, et al. (2014)Novel anti–B-cell maturation antigen antibody-drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. Blood 123: 3128-3138.
19. Chiu A, Xu W, He B, Dillon SR, Gross JA, Set al. (2007) Hodgkin lymphoma cells express TACI and BCMA receptors and generate survival and proliferation signals in response to BAFF and APRIL. Blood 109: 729-739.
20. Carpenter RO, Evbuomwan MO, Pittaluga S, Rose JJ, Raffeld M, et al. (2013) B-cell maturation antigen is a promising target for adoptive T-cell therapy of multiple myeloma. Clin. Cancer Res 19: 2048-2060.
21. Cho SF, Lin L, Xing L, Wen K, Yu T, et al. (2019) AMG 701 Potently Induces Anti-Multiple Myeloma (MM) Functions of T Cells and IMiDs Further Enhance Its Efficacy to Prevent MM Relapse In Vivo. Blood 134.
22. Pratz KW (2017) Blinatumomab induced response of multiply refractory multiple myeloma in the context of secondary pre-B cell acute lymphoblastic leukemia. Ann Hematol Oncol. (2017) 4:1174 10.26420/annhematoloncol 1174.
23. Hönemann D, Kufer P, Rimpler MM, Chatterjee M, Friedl S, et al. (2004) A novel recombinant bispecific single-chain antibody, bscWue-1 x CD3, induces T-cell-mediated cytotoxicity towards human multiple myeloma cells. Leukemia 18: 636-644.
24. Ramadoss NS, Schulman AD, Choi SH, Rodgers DT, Kazane SA, et al. (2015) An anti-B cell maturation antigen bispecific antibody for multiple myeloma. J Am Chem Soc 137: 5288-5291.
25. Zou J, Chen D, Zong Y, Ye S, Tang J, et al. (2015) Immunotherapy based on bispecific T-cell engager with hIgG1 Fc sequence as a new therapeutic strategy in multiple myeloma. Cancer Sci 106: 512-521.
26. Hipp S, Tai YT, Blanset D, Deegen P, Wahl J, et al. (2017) A novel BCMA/CD3 bispecific T-cell engager for the treatment of multiple myeloma induces selective lysis in vitro and in vivo. Leukemia 31: 2278.
27. Seckinger A, Delgado JA, Moser S, Moreno L, NeuberB, et al. (2017) Target expression, generation, preclinical activity, and pharmacokinetics of the BCMA-T cell bispecific antibody EM801 for multiple myeloma treatment. Cancer Cell 31: 396-410.
28. Durben M, Schmiedel D, Hofmann M, Vogt F, Nübling T, et al. (2015) Characterization of a bispecific FLT3 X CD3 antibody in an improved, recombinant format for the treatment of leukemia. Mol Ther 23: 648-655.
29. Pratz KW (2017) Blinatumomab induced response of multiply refractory multiple myeloma in the context of secondary pre-B cell acute lymphoblastic leukemia. Ann Hematol Oncol 4: 1174.