

REVIEW

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Blinatumomab: a bispecific T cell engager (BiTE) antibody against CD19/CD3 for refractory acute lymphoid leukemia

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Abstract

Targeted therapy has been the forefront of cancer treatment. Cancer immunotherapy is the most recent focus. In addition, novel immunotherapeutics targeting B cell receptor signaling (e.g., ibrutinib), T cell receptor (e.g., CART19), and NK cells (e.g., AFM13) are being developed. This review summarized the new development in blinatumomab (MT103/MEDI-538), a first-in-class bispecific T engager (BiTE) antibody against CD19/CD3 in patients with relapsed/refractory precursor B cell acute lymphoid leukemia.

Targeted therapy has been the forefront of cancer treatment [1–7]. Monoclonal antibodies have played a major role in lymphoma therapy for more than a decade [8–11]. Cancer immunotherapy is the most recent focus of clinical development [12–17]. In addition, novel immunotherapeutics targeting B cell receptor signaling (e.g., ibrutinib) [2, 18], T cell receptor (e.g., CART19) [19–22], and NK cells (e.g., AFM13) [23–25] are being developed. This review summarized the clinical development in blinatumomab (MT103/MEDI-538), a first-in-class bispecific T engager (BiTE) antibody against CD19/CD3 in patients with relapsed/refractory precursor B cell acute lymphoid leukemia (ALL).

Bispecific antibodies and diabody

Bispecific antibodies (bsAb) was initially developed through hybrid-hybridoma, chemical linkage, or renaturation from purified recombinant Fab or Fv fragment from bacterial inclusion bodies [11, 26, 27]. One of the major limitations of these technologies is the difficulty in producing sufficient amount of clinical grade bsAbs. This has made the clinical testing of the bsAbs falling behind.

Through molecular cloning and/or phage expression library, high affinity recombinant single-chain Fv

fragment (scFv) has been produced. This led to the development of bivalent bispecific antibody fragments, diabodies [11, 26, 27]. A heavy chain scFv (V_H) is connected with a light chain scFv (V_L) by a short amino acid linker to form a single polypeptide. The short linker is too short to allow self association of the two adjacent V_H and V_L domain. Therefore, by linking the V_H and V_L of two different antibodies A and B to form two different “cross-over” polypeptide chain V_HA-V_LB and V_HB-V_LA , a diabody containing both antigen-binding sites through non-covalent association is formed (Fig. 1) [11, 26, 27]. One such functional small bispecific antibody against EpCAM /CD3 was engineered and purified from Chinese hamster ovary (CHO) cells [27]. This antibody was found to be able to redirect T cells to lyse colon cancer cells expression EpCAM antigen. Using this approach, clinical grade bsAbs were produced from CHO cells in large quantity [23, 24, 28].

Structure and properties of blinatumomab

Combination chemotherapy for relapsed and/or refractory acute lymphoblastic leukemia usually leads to a CR rate in 30–45 % of patients and overall survival of 4.7–8.6 months in first salvage treatment [29–33]. CD19 is a common B cell surface marker [34–38]. Monoclonal antibodies against CD19 have been in active clinical development [39, 40].

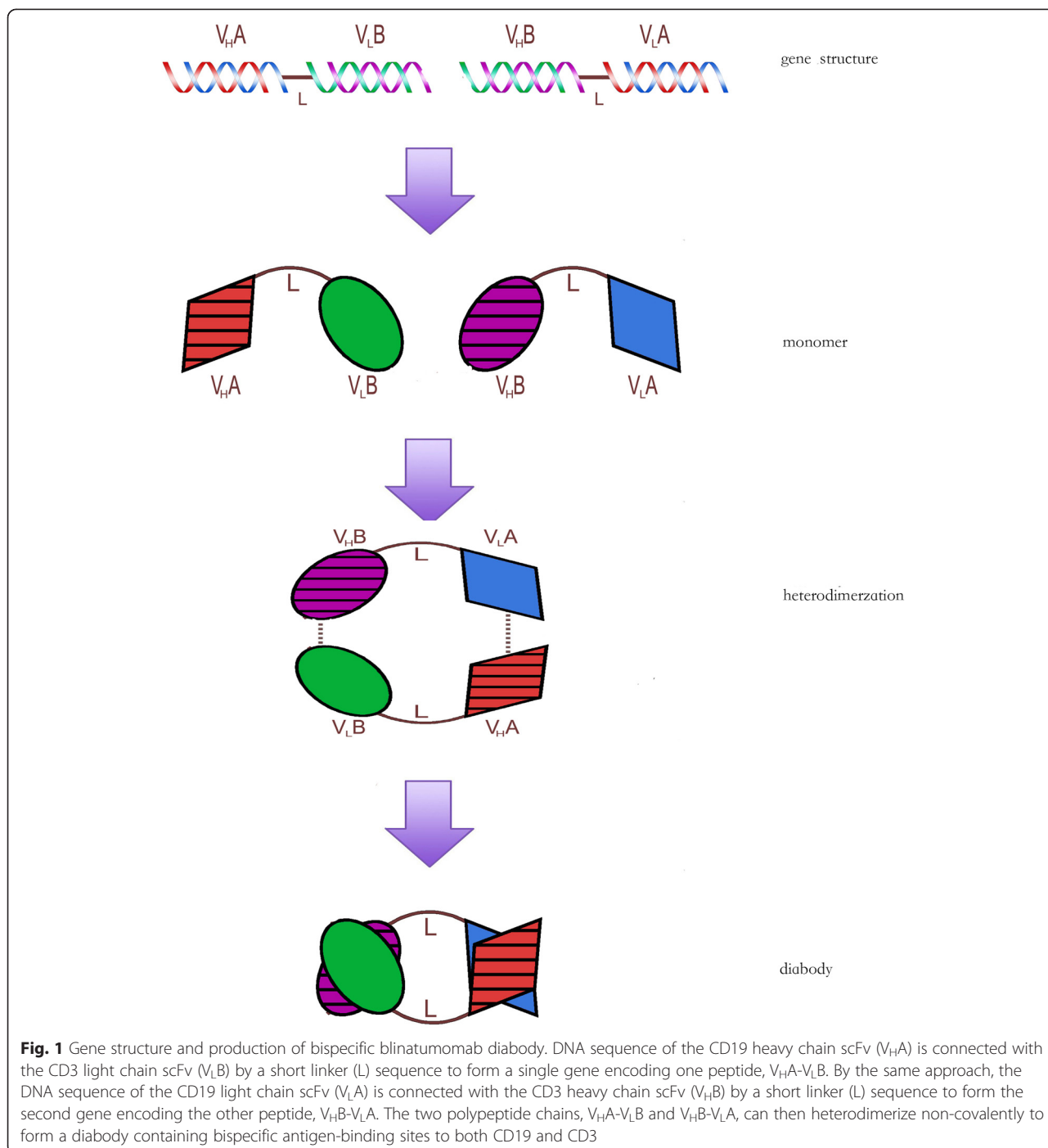
In an attempt to develop novel treatment agent for refractory B cell malignancies, a bsAb against CD19/CD3,

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MT103/MEDI-538 (blinatumomab), was engineered using the diabody approach [41]. One arm of this antibody binds CD19, while the other arm binds CD3 (Fig. 2). By redirecting unstimulated primary human T cells against CD19-positive lymphoma cells, the bispecific CD19/CD3 antibody fragment showed significant cytotoxic activity at very low concentrations of 10 to 100 pg/mL and at effector-to-target cell ratios as low as 2:1. This single-chain bispecific antibody construct belongs to a new class of antibody

fragments, BiTE [42–51]. This bispecific antibody fragment has a molecular weight of 54.1 kDa, approximately one-third of the size of a traditional monoclonal antibody (mAb). As CD19 is an attractive target, CD19 mAb has been widely studied for therapies of lymphoma, leukemia, and autoimmune disorders, such as anti-B4-bR, SAR3419 (huB4-DM4), and BiTE [38–40, 52]. Blinatumomab can potentiate unstimulated T cells and induce direct cytotoxicity against CD19+ cells [42].

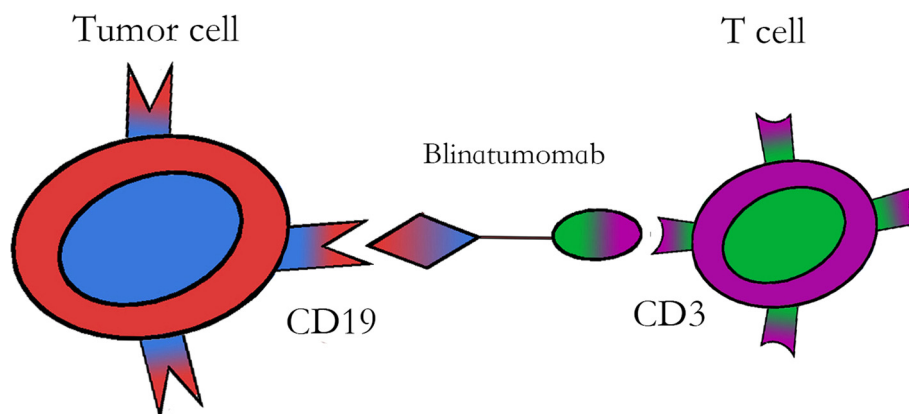


Fig. 2 Mechanism of action for blinatumomab as the first-in-class bispecific T cell engager (BiTE). One arm of blinatumomab binds to CD3, the other binds to CD19. This engages the unstimulated T cells which destroy the CD19+ cells

Several properties of blinatumomab promoted its development for immunotherapy of lymphoma and leukemia. Because of its single-chain structure, blinatumomab can be produced with a stable purified monomeric formulation in large quantities for clinical use [23, 24, 28, 41]. Blinatumomab has been shown to increase inflammatory cytokine production, specifically IL-2, IFN- γ , TNF- α , IL-4, IL-6, and IL-10 [53]. Importantly, it can bridge malignant B cells directly to CD3-positive T cells, bypassing T cell receptor (TCR) specificity and major histocompatibility complex (MHC) class I molecules [41, 54, 55]. The CD19/CD3 BiTE antibody was shown to induce T-cell-mediated depletion of primary lymphoma cells in 22 out of 25 cases. This effect could be observed at low effector-to-target (E:T) ratios and in the majority of cases without additional activation of autologous T cells by IL-2 [41, 54]. Data from animal models support a high activity of blinatumomab at very low doses against tumor cells in lymphoma and leukemia models [43, 48, 55–57].

Blinatumomab in clinical development

Blinatumomab is the first-in-class BiTE antibody approved for treatment of refractory ALL [46, 47, 58–64].

Blinatumomab was first reported in a clinical phase I trial in 38 patients with refractory non-Hodgkin lymphoma [58]. Due to its short half-life and mechanism of action, blinatumomab was given as continuous intravenous infusion (CIV) in the study MT103-104 (NCT00274742). The doses ranged from 5 to 60 $\mu\text{g}/\text{m}^2/\text{day}$ over a period of 4–8 weeks. The maximum tolerated dose (MTD) of blinatumomab was reported to be 60 $\mu\text{g}/\text{m}^2/\text{day}$. This study first demonstrated the efficacy of blinatumomab in B cell malignancies. Eleven of 38 patients (28.9 %) had measurable response after treatment, including 4 (11 %) CR and 7 (18 %) PR. The most commonly observed adverse events (AEs) were pyrexia, chills, and leucopenia. CNS toxicity and cytokine release syndrome (CRS) were observed [58].

By 2011, 62 patients had been enrolled in this study with an objective response of 18/22 (82 %) and 32-month response duration. Blinatumomab treatment at doses of $\geq 15 \mu\text{g}/\text{m}^2/\text{day}$ led to depletion of tumor cells in blood, lymph nodes, spleen, and bone marrow [58]. During or after treatment, T cell counts remained stable or increased. Blinatumomab treatment predominantly caused an expansion of effector memory CD8+ and CD4+ T cells with CD45RA/CCR7 phenotype. It was also observed that there was an early disappearance of T cells. This may be due to a transient increase in the adhesiveness of T cells to vessels and/or extravasation. No clinically significant cytokine release syndrome was seen in any patient. There was no autoimmune disorder observed with blinatumomab treatment. Neutralizing antibodies against blinatumomab was not detected in these patients [58].

A single-arm phase II study (MT103-206, NCT01209286) evaluated response to blinatumomab in molecularly relapsed/refractory precursor B cell ALL [61]. In this study, a total of 36 patients were treated. A dose-finding component followed by an extension cohort from 5 (week 1) to 15 $\mu\text{g}/\text{m}^2/\text{day}$ on subsequent 3 weeks was included. A 2-week treatment-free interval followed the completion of the 4-week continuous infusion of blinatumomab to allow T cell recovery. CR or CRh (incomplete hematological recovery) was observed in 25 of 36 patients (69 %), and 22 of 25 responders (88 %) achieved a molecular remission. Response was better in patients in first relapse than those in second or greater relapse. Median relapse-free survival (RFS) was 7.6 months, with a 9.8-month median overall survival (OS). With a median follow-up of 405 days, the probability of RFS was 78 %. The most frequent grade 3 and 4 adverse event was lymphopenia, which was reversible. These results are encouraging compared to the median OS of 6 months in relapsed ALL with chemotherapy [61]. Among patients with longer follow-up (median 33 months), 80 % response

rate with minimal residual disease (MRD) was reported [65]. Among the 6 Philadelphia chromosome-negative MRD responders, 4 remained in hematologic and molecular remission with no further therapy after blinatumomab. Therefore, blinatumomab can induce long-lasting complete remission in B-lineage ALL patients with persistent or recurrent MRD [65–67].

Subsequently, a large, multicentre, phase II trial (MT103-211, NCT01466179) assessed blinatumomab in 189 adult patients with relapsed or refractory B cell ALL [62, 68]. These patients were negative for Philadelphia chromosome and had primary-refractory disease, early first relapse, or multiple relapses. The trial also enrolled patients who had relapsed within 12 months after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Patients received blinatumomab as continuous intravenous infusion with a flat dose of 9 $\mu\text{g}/\text{day}$ at week 1 (cycle 1 only, to reduce cytokine release syndrome) and 28 $\mu\text{g}/\text{day}$ for 3 weeks. This was followed by a 2-week treatment-free interval. Therefore, each cycle was 6 weeks, and patients received treatment up to 5 cycles in the study. Premedication with dexamethasone (20 mg) within 1 h of treatment initiation in each cycle and before the dose step-up in cycle 1 was given to minimize infusion reactions to blinatumomab. However, high-dose (≥ 24 mg) dexamethasone was only allowed for 7 days or less. The infusion was allowed to be interrupted for AEs grade 3 or higher and resumed after reduction of AEs to grade I or complete resolution. The clinical response in the first 2 cycles was 33 % CR (63 of 189 patients) and 10 % CRh (18 of 189 patients), with 40 % (32 of 81 patients in CR/CRh) went on to receive allo-HSCT. Median relapse-free survival was 5.9 months for those patients who achieved CR/CRh, with a median OS of 6.1 month for all 189 patients [68]. Among the 73 responders with available data on MRD, 80 % of patients achieved MRD negativity [69]. The relative odds ratio by Mantel-Byar analysis for survival benefit of achieving remission was 0.13 ($p < 0.0001$). Responses in patients older than 65 years and in those who received previous allo-HSCT were noted. These two patient groups for whom treatment options are very limited due to substantial toxicity associated with currently available polychemotherapies. Common AEs associated with blinatumomab such as febrile neutropenia, neutropenia, and anemia were consistent with those previously reported. CRS in grade 3 occurred in 3 (2 %) patients [68, 70]. Neurologic events, including tremors, seizure, and mental status change, were seen in 98 (52 %) patients, mostly in grade 1 or 2, with 20 (11 %) in grade 3 and 4 (2 %) in grade 4. In these patients with high-risk features, 40 % of them went on to allo-HSCT (17 % for those with prior transplantation, 52 % with no prior transplantation). There were patients who had response to blinatumomab but did not receive allo-

HSCT because they were ≥ 65 or had prior HSCT that precluded them from allo-HSCT [71].

In a separate confirmatory trial, BLAST trial, 116 adult patients (median age 45, range 18–76) with MRD+ pre-B ALL were treated with continuous IV infusion of blinatumomab at 15 $\mu\text{g}/\text{m}^2/\text{day}$ in a similar schedule (4-week treatment, 2-week rest) as described above [72]. The MRD negative response rate was 78 % (95 % CI, 69–85 %) after 1 cycle of treatment. The results appeared to be consistent with those from previous studies [65, 68].

Blinatumomab was also studied in pediatric patients with relapsed/refractory pre-B ALL in a phase I/II clinical trial [73]. Patients received blinatumomab for 4 weeks by continuous IV infusion followed by a 2-week treatment-free period (for up to 5 cycles). Escalating dosing levels of 5, 15, and 30 $\mu\text{g}/\text{m}^2/\text{day}$ and stepwise dosing of 5–15 or 15–30 $\mu\text{g}/\text{m}^2/\text{day}$ were evaluated. In the phase I portion, 41 patients were treated. A total of 13 (32 %) patients achieved CR with 10 (77 %) achieving MRD negativity. Of these 13 patients, 9 (69 %) went on to have HSCT. The adverse events as well as pharmacokinetic data, including steady-state concentration, clearance, and half-life were similar to those from adult patients with relapsed/refractory BCP-ALL who received body surface area-based dosing. The MTD was 15 $\mu\text{g}/\text{m}^2/\text{day}$ in the pediatric patients. Stepwise dosing was useful in reducing CRS. The 5 (week 1) to 15 $\mu\text{g}/\text{m}^2/\text{day}$ (week 2 to 4) step-wise dosing was therefore used for phase II portion of the study. At the time of last update, 39 patients were treated at this dose (median age 9, range 2–18) [74]. Blinatumomab showed promising antileukemia activity in this group of high-risk pediatric relapsed/refractory B cell precursor ALL patients. Among patients who had remission after the first 2 cycles of blinatumomab single-agent therapy, half went on to receive allo-HSCT. Therefore, blinatumomab may create a window for allo-HSCT for those patients who are resistant to salvage chemotherapy [73–75].

Conclusion and future directions

Blinatumomab represents the first-in-class BiTE antibody in clinical use and provides a novel therapeutic option for patients with relapsed/refractory B cell ALL [43, 58, 64, 67, 76]. The pharmacodynamics and immunophenotype data are still being collected [67]. One obvious disadvantage of this BiTE antibody is the requirement for continuous IV infusion because of the small molecular weight and rapid clearance from circulation. Newer tetravalent bispecific antibodies, AFM11 and AFM13, can be given as weekly or twice weekly [23, 24, 28]. T cells with CD19/CD3 chimeric antigen receptors (CAR-T) have been shown to induce high remission rate (90 % CR in refractory ALL), and can expand 1000 times in vivo [77–80]. The rate of CRS associated with CAR-T therapy

(27 % severe) was much higher than that of blinatumomab (2 %). CAR-T was shown to penetrate blood-brain barrier [78]. It is not known whether blinatumomab has similar property. It remains unclear what is the optimal treatment duration and schedule of blinatumomab for patients who cannot receive allo-HSCT. The role of consolidation or maintenance for blinatumomab also remains an area of investigation. Incorporation of blinatumomab in the first-line treatment setting is in active clinical trials (NCT02143414, phase II and NCT02003222, phase III). BiTE antibodies against other antigens (e.g., CD33, CD 79b) are under active clinical studies for myeloid leukemia and lymphoma [81, 82]. Since blinatumomab was shown to activate effector T cells [52, 58], it would be interesting to study the potential of using blinatumomab for effector T cell expansion for cancer immunotherapy.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DL designed the study. JW and DL drafted the manuscript. DL and JF designed and finalized the figure preparation. All authors were involved in manuscript preparation and revisions. All authors read and approved the final manuscript.

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