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Bispecific Antibodies in Hematologic Malignancies: When, to Whom, and How Should Be Best Used?

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Abstract

Purpose of Review The purpose of this review is to discuss the current recommendations for the use of bispecific antibodies (bsAb) in hematologic malignancies and explore the future in this field.

Recent Findings Bispecific antibodies are molecules able to target two different antigen-binding sites: one towards a tumor antigen and another to activate a cytotoxic cell. Phase II/III trials on blinatumomab for acute lymphoblastic leukemia (ALL) have demonstrated its efficacy for treating minimal residual disease (MRD+) and relapsed refractory (r/r) Philadelphia positive (Ph+) and negative (Ph−) ALL in adults and children.

Summary Currently, the only bispecific antibody (bsAb) approved for its use in hematologic malignancies is blinatumomab. However, multiple trials are under development not only to explore blinatumomab's clinical activity in other neoplasia, such as lymphoma or multiple myeloma, but also to develop new molecules against different antigens.

Keywords Antibodies · Bispecific antibodies · Antineoplastic agents · Immunotherapy · Acute lymphoblastic leukemia · T-lymphocytes

Introduction

Based on the evidence that the immune system plays a major role in tumor-specific cellular responses, cancer immunotherapy has been evolving quickly over the last decades, being of paramount importance in the cancer drug armamentarium. Currently, the main types of immunotherapy being used to treat cancer include monoclonal antibodies (mAbs), chimeric antigen receptor T cells (CAR T), immune checkpoint inhibitors, and cancer vaccines [1].

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Monoclonal antibodies are monospecific bivalent molecules that bind the same antigen fragment (epitope), widely used for different types of cancer. However, mAbs as monotherapy are not able to cure as they do not activate T-lymphocytes that have an active part in the destruction of cancer cells [2]. Bispecific antibodies are mAbs conformed by two antigen-binding sites: one directed against a receptor that activates cytotoxic cells and the other against an specific antigen expressed by tumor cells [3•].

In the early 1960s, pioneers in the antibody engineering started working in the idea of a bsAb; however, it was until 1985 when the first bsAb was constructed [3•]. Since then, diverse bsAb have been manufactured, being on 1995 the first time that a bsAb entered a clinical trial for a hematologic malignancy, a CD19 and CD3 binding antibody for non-Hodgkin lymphoma (NHL) [4].

To date, there are only two bsAb with approval by the US Food and Drug Administration (FDA): blinatumomab initially approved in 2014 for acute lymphoblastic leukemia (ALL) and emicizumab approved for hemophilia A in 2017. The purpose of this review is to discuss the current recommendations for the use of bsAb in hematologic malignancies and explore the future in this field.

What Are Bispecific Antibodies?

The technology for the construction of bsAb has progressed since their first construction, having today more than 100 different formats suitable for diagnosis and therapy [5•]. Bispecific antibodies can be differentiated according to their function in those that act directly on their targets to activate or neutralize them or those that use their target to deliver a therapeutic active molecule. Regarding the structure of bsAb, they can overall be categorized in two major types, "IgG-like" and "non-IgG-like" based on the presence or absence of a fragment crystallizable (Fc) region [6]. Antibodies lacking the Fc region are also called bifunctional and are variable domain-only antibodies like bispecific T cell engager (BiTE), dual-affinity re-targeting (DART), and tandem antibodies (TandAb) [7]. The IgG-like bsAb are also called trifunctional and can be discriminated by the number of binding sites (bivalent to tetravalent) [5•, 7].

The use of bsAb as a type of cancer therapy is primarily due to their ability of recruiting immunologically competent cells, T cells by CD3, NK cells by CD16, monocytes and macrophages by CD64, and/or granulocytes by CD89, and redirects them to a target to start tumor lysis [7]. Blinatumomab is the only approved bsAb for its use in patients with hematologic malignancies.

Blinatumomab

Blinatumomab also called MT103 is a 55-kDa BiTE directed to CD19 (B cell differentiation antigen) and CD3 (T cell receptor) receptors. These receptors are linked, and its synapse causes release of inflammatory cytokines, production of cytolytic proteins, and proliferation of T cells, resulting in lysis of CD19 B cells. In humans, it was first explored in relapsed-refractory NHL and chronic lymphocytic leukemia (CLL) and afterwards in ALL [8–10].

However, based on trial results, the only current approved indication is ALL in three distinct settings: positive minimal residual disease (MRD+), refractory and relapsed (r/r) Philadelphia negative (Ph−), and r/r Ph positive (Ph+), in both pediatric and adult ALL patients (Table 1).

ALL MRD+

The first study made in B cell lineage ALL was a phase II trial that included patients in complete remission (CR) but with persistent MRD. A total of 21 patients in CR with molecular failure or molecular relapse at any point after first consolidation of frontline chemotherapy regimen within the protocols of the German Multicenter Study Group for Adult ALL (GMALL) were included. Among 20 evaluable patients, 80% ($n = 16$) achieved MRD-negative (MRD−) status within 4 cycles of treatment and 61% ($n = 12$) sustained CR and MRD− after a median observation time of 33 months. In this study, all eligible patients were offered an allogeneic hematopoietic stem cell transplant (alloHSCT) after the first cycle of blinatumomab; nine patients underwent transplant with a relapse-free survival (RFS) of 65% with only one transplantation-related death, suggesting that the sequence blinatumomab-alloHSCT is not related to excessive treatment-related mortality [11].

In the basis of the previous results, a confirmatory open-label, single-arm, phase II, multicenter trial to assess efficacy and tolerability of blinatumomab in adult patients with MRD+ ALL was developed. Compared to the pilot study, level of MRD was higher ($\geq 10^{-3}$ vs. $\geq 10^{-4}$) and the proportion of MRD+ patients after relapse was greater. A total of 116 patients were included, 113 were evaluable, and 88 (78%) achieved MRD− status. The RFS at 18 months was 54%, and median overall survival (OS) was 36.5 months. Complete MRD responders had longer RFS (23.6 vs. 5.7 months; $p = .002$) and OS (38.9 vs. 12.5 months; $p = .002$) compared to persistent MRD+ patients. With a median follow-up of 24 months, 25% ($n = 9$) of the patients that did not receive alloHSCT or any chemotherapy after blinatumomab remained in CR compared to 49% ($n = 36$) of the patients that underwent alloHSCT [12].

Relapsed/Refractory Ph− ALL

In 2011, the results of three pediatric patients with post-alloHSCT r/r ALL treated with blinatumomab in a compassionate use program were reported; all three patients achieved a complete molecular response [13]. Soon, the need to further investigate the use of blinatumomab in this scenario was clear.

Between 2010 and 2012, a total of 36 patients were enrolled in a phase II trial performed to determine clinical activity of blinatumomab in adult patients with r/r ALL. Twenty-five (69%) patients achieved CR or CR with partial hematologic recovery (CRh), and 88% of these responders achieved a MRD− status. Median OS was 9.8 months (95% IC, 8.5–14.9), and median RFS was 7.6 months (95% IC, 4.5–9.5). Thirteen responders (52%) underwent alloHSCT with seven long-term survivors, compared to four survivors from the 12 patients that did not receive alloHSCT [14].

To confirm the clinical activity and safety profile of blinatumomab in ALL adult patients, a multicenter, single-arm, phase II study enrolled 189 patients with r/r Ph− ALL. After 2 cycles, 81 (43%) patients achieved a CR or CRh; 33% had a CR, and 10% had a CRh. Median RFS was 5.9 months (95% CI, 4.8–8.3), and median OS was 6.1 months (95% CI,

Table 1 Results of blinatumomab clinical trials on approved FDA indications for ALL

Author (year)	Trial indication	Number	MRD− (%)	Median OS (months)	Median RFS (months)
Topp et al. (2012)	Phase II MRD+	21	80	NR	61% at 33 months
Gökbuget et al. (2018)	Phase II MRD+	116	78	36.5	18.9
Topp et al. (2014)	Phase II Adult r/r Ph− ALL	36	61	9.8	7.6
Topp et al. (2015)	Phase II Adult r/r Ph− ALL	186	35	6.1	5.9
Kantarjian et al. (2017)	Phase III Adult r/r Ph− ALL	271	35	7.7	7.3
Von Stackelberg et al. (2016)	Phase I/II Pediatric r/r Ph− ALL	70	20	7.4	4.3
Martinelli et al. (2017)	Phase II r/r Ph + ALL	45	32	7.1	6.7

MRD minimal residual disease, *OS* overall survival, *RFS* relapse-free survival, *NR* not reported, *r/r* relapsed/refractory, *Ph* Philadelphia, *ALL* acute lymphoblastic leukemia

4.2–7.5). Adverse events were consistent with the previously reported including influenza-like syndrome, such as pyrexia. Events of cytokine release syndrome were uncommon, and no patient in remission had a fatal adverse event suggesting that despite the advanced stage of the included individuals, blinatumomab is associated with low treatment-related mortality [15].

Once antileukemic activity of blinatumomab was proven, it was compared to standard chemotherapy in a multicenter, phase III trial (TOWER). A total of 405 patients with heavily pretreated B cell ALL were randomly assigned to receive blinatumomab (271 patients) or standard salvage chemotherapy (134 patients). Remission rates within 12 weeks after treatment initiation were higher in the blinatumomab group, both for CR and CRh (34% vs. 16%, $p < .001$; 44% vs. 25%, $p < .001$, respectively). Overall survival was significantly longer in the blinatumomab group compared to the chemotherapy group, 7.7 months vs. 4.0 months (HR 0.71; 95% CI, 0.55–0.93; $p < .01$). Blinatumomab resulted in higher 6-month RFS (31% vs. 12%; HR 0.55; 95% CI, 0.43–0.71; $p < .001$) as well as longer median duration of CR (7.3 vs. 4.6 months). A total of 24% of the patients in each treatment group underwent alloHSCT; mortality was similar in both the blinatumomab and the chemotherapy groups (26% and 25%, respectively). Adverse events of grade 3 or higher were reported in 87% of patients treated with blinatumomab and 92% of patients treated with chemotherapy [16•].

For pediatric patients, the first trial demonstrating antileukemic activity of blinatumomab was a global open-label, phase I/II trial designed to evaluate the efficacy in children with r/r B cell precursor ALL. Seventy patients were treated; 27 (39%) patients achieved CR within the first 2 cycles, 14 (52%) of whom achieved MRD− status [17•].

Relapsed/Refractory Ph+ ALL

Blinatumomab has also been evaluated in Ph+ ALL. A phase 2, single-arm, multicenter study evaluated the efficacy and tolerability of blinatumomab in patients with r/r Ph+ ALL. It included 45 adult patients who relapsed after, were refractory or intolerant to imatinib, and/or were refractory or intolerant to at least 1-s generation or later tyrosine kinase inhibitors (TKIs). Sixteen patients (36%; 95% CI 22–51%) achieved CR/CRh during the first 2 cycles, including 10 patients with T315I mutation. An 88% of responders achieved a complete MRD− response. Seven responders (44%) underwent alloHSCT. The median RFS and OS were 6.7 months and 7.1 months, respectively [18].

Also, a retrospective study has been published about blinatumomab in combination with TKIs in the treatment of r/r Ph+ ALL, indicating that this combination may be safe and effective, although prospective studies are warranted [19]. A phase II study of the combination of blinatumomab and bonatinib in patients with Ph+ and/or *BCR-ABL*-positive ALL is currently ongoing (NCT03263572).

How Blinatumomab Should Be Administrated?

Blinatumomab is administrated as a continuous IV infusion over 4 weeks followed by a treatment-free period of 2 weeks. Up to 5 cycles (4 cycles for the MRD scenario) can be administrated if CR is achieved after 1 or 2 cycles. In the TOWER phase III trial, 10% of the patients received four extra cycles of continued therapy (cycles 6 to 9) administrated every 3 months [16•]. Most of blinatumomab's adverse events (AEs) are mild to moderate and occur during the first cycle; thus, treatment schedule begins with a lower dose for the first 7 days and

requires in patient observation. Chills, pyrexia, constitutional symptoms, and reversible neurologic events such as tremors, seizures, aphasia, and ataxia are the most frequently seen AEs [15]. Cytokine release syndrome which may be life-threatening has occurred but is uncommon. To minimize these, administration demands premedication with dexamethasone during the first day of every cycle and the first day of any dose escalation [15, 16•, 20].

Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

As we already mentioned, the first trials of blinatumomab were performed in patients with NHL and CLL. There are only few studies evaluating blinatumomab in patients with NHL. Early clinical data from a phase 1 clinical trial showed activity in 76 patients with different NHL subtypes in the r/r setting [10]. The best responses were seen in follicular lymphoma, with 80% overall response rate (ORR) and 40% achieving CR. Specifically in diffuse large B cell lymphoma, a phase 2 clinical trial in the r/r setting showed ORR of 43%, with CR of 19% and progression-free survival (PFS) of 3.7 months in the evaluable patients [21]. The doses used in these studies were higher than those used for ALL. The maximum tolerated dose from the phase 1 study was 60 mcg/m^2/day, and the dose for the phase 2 trial was 112 mcg/day, both in continuous infusion and weekly dose escalation. More trials are still needed to assess AEs and tolerability.

In CLL, since 2003, there is in vitro evidence of the activity of blinatumomab against CLL cells [22, 23]. However, we still do not have evidence of its clinical activity.

Blinatumomab Ongoing Studies

Studies with blinatumomab are running in different scenarios. For ALL, blinatumomab in first line is being combined with different chemotherapy regimens (NCT03480438, NCT03518112, NCT03541083, NCT02877303, NCT02143414), and with TKIs in Ph+ ALL (NCT02003222, NCT02744768). Also, the role of blinatumomab for maintenance after alloHSCT is being assessed (NCT02807883). In the r/r setting, blinatumomab is being combined with PD-1/PD-L1 inhibitors: bembrolizumab (NCT03160079, NCT03340766, NCT03512405), bivolumab ± ipilimumab (NCT02879695), and with ibrutinib (NCT02997761).

For CLL/NHL, studies are ongoing for Richter transformation (NCT03121534, NCT03072771), MRD treatment in DLBC NHL after autologous HSCT (NCT03298412), r/r indolent or agressive NHL (NCT02811679, NCT02910063), r/r indolent NHL as subcutaneous formulation (NCT02961881), first line in DLBC NHL (NCT03023878), and in combination with lenalidomide in r/r NHL (NCT02568553). Also, a study of blinatumomab for r/r multiple myeloma is being conducted (NCT03173430).

Other Bispecific Antibodies Under Development

Antibodies for ALL and Lymphomas

AFM11 is a tetravalent bispecific TandAb with two binding sites for CD3 and two for CD19 that has shown potent in vitro cell lysis [24]. Another advantage of this construct is a longer half-life of 20 h. AFM11 is now being tested in phase 1 studies for r/r ALL and NHL. MGD011 (duvortuxizumab) is a CD19/CD3 DART with an extended half-life, allowing weekly of biweekly IV administration [25]. It has been tested in phase 1 studies alone or in combination with ibrutinib in B cell malignancies (NCT02454270, NCT02743546), but the higher rate of neurotoxicity led to early termination of one of the trials. FBTA05 is a trifunctional antibody construct binding to CD3 on T cells and CD20 on malignant B cells; the third functional site within the hybrid Fc region binds to Fcγ receptor type I, IIa, and III which are expressed by accessory immune cells [26]. There are ongoing clinical trials for this construct and some case reports in pediatric patients showing a promising response [27, 28]. REGN1979 is a CD3/CD20 bispecific antibody based on a IgG4 isotope modified to reduce Fc binding. In a phase 1 study, 38 R/R NHL patients were treated with 12 weekly doses followed by maintenance with 12 every 2-week doses. The ORR was 45%. The more frequent adverse events were pyrexia (66%), chills (50%), and cytokine release syndrome (CRS) (42%). There was no clinical significant neurologic toxicity [29]. In another phase 1 study, ten NHL patients were treated with REGN1979 in combination with a PD-1 monoclonal antibody; they had some PR with 89% of CRS [30]. Two new constructs (RG6026 and RG7828) with two domains for CD20 and one domain for CD3, with a more potent CD20 activity, are now on phase 1 clinical trials [31]. Finally, AFM13, a CD30/CD16A tetravalent chimeric construct, has been developed for CD30-expressing malignancies. It recruits NK cells via CD16A. In a phase 1 trial in R/R Hodgkin lymphoma, 28 patients were treated. The only dose-limiting toxicity was hemolytic anemia. The PR was 11.5%, but in the group of patients receiving a dose ≥ 1.5 mg/kg, PR was 23% [32].

Multiple Myeloma

The B cell maturation antigen (BCMA) is a highly plasma cell-selective protein expressed on myeloma cells and has been successfully targeted by CAR T cell therapy. Some bsAb have been developed targeting BCMA and are now on clinical trials (NCT02514239, NCT03269136,

NCT03145181). One of them, AMG420, a BiTE, has been shown to be very active against myeloma cells in preclinical studies [33]. EM801 is a trivalent bsAb with two binding sites for BCMA and one for CD3 [34]. Also, some bsAb directed against CD38 or the tumor-associated antigen Fc receptor-like protein 5 (TCRH5) which is overexpressed in myeloma cells are under development [35–37].

Acute Myeloid Leukemia

Diverse bsAb have been developed against different antigens in acute myeloid leukemia, including CD33, CD123, Wilms' tumor protein (WT1), CD13, CD15, CD30, CD45, CD47, C-type lectin-like molecule 1 (CLL1), Fms-like tyrosine kinase 3 (FLT-3), and angiogenic growth factors [38]. AMG 330 is a BiTE directed against CD33/CD3. The results of the phase 1 clinical trial have not been presented (NCT02520427). Data suggest that in some cases, T cell activation and cytotoxicity were suboptimal because of inhibition by the PD-1/PDL-1 pathway and the inhibition of this pathway can restore T cell citotoxicity [39–41]. Also, the use of epigenetic modifiers such as azacitidine or panobinostat can increase CD33 expression [41].

Flotetuzumab is a CD123/CD3 DART. In a phase 1 clinical trial, 45 patients with R/R AML and MDS were treated and the ORR was 43% with a manageable safety profile [42]. In a similar way, there is evidence suggesting a synergistic role of combining flotetuzumab with anti-PD-1/PD-L1 immunotherapies [43].

Conclusion

Immunotherapy is nowadays a fundamental tool for cancer therapy and a growing area. Understanding the structure of bsAb and how this can be manipulated to impact in the antitumor mechanisms, without increased AEs, is a challenge for clinical researchers. Combined therapies with mAbs, other targeted molecules, and emerging immunotherapy are in the sight as promising tools for the future of hematology.

Compliance with Ethical Standards

Conflict of Interest Roberta Demichelis-Gómez has received research funding through grants from Amgen and Novartis; has received speakers' honoraria from AbbVie, Amgen, Celgene, Novartis, and Shire; has received reimbursement for travel expenses from AbbVie and Amgen; and has received compensation from AbbVie and Novartis for participation on advisory boards.

Daniela Pérez-Sámano declares that she has no conflict of interest.

Christianne Bourlon has received speakers' honoraria from Shire.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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