Bispecific Antibodies in Non-Hodgkin's Lymphoma

Subjects: Hematology

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Bispecific antibodies (bsAbs) are molecules that simultaneously bind two different antigens (Ags). Their development represents a very active field in tumor immunotherapy with more than one hundred molecules currently being tested. More specifically, bsAbs have elicited a great interest in the setting of non-Hodgkin's lymphomas (NHLs), where they could represent a viable option for more fragile patients or those resistant to conventional therapies.

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1. Blinatumomab

Blinatumomab, an anti-CD19/CD3 bispecific T-cell engager (BiTE), was the first bsAb to show high efficacy in the relapsed/refractory (R/R) setting of B-cell acute lymphoblastic leukemia (B-ALL) and was approved by the Federal Drug Administration (FDA) for this indication in 2014[1][2]. In addition, it has also been assessed as a salvage strategy in R/R non-Hodgkin's lymphoma (NHLs)[3][4][5].

In a phase 1 study, Blinatumomab was used as a continuous infusion (for four to eight weeks, plus an additional four weeks if clinical benefit was achieved) with an escalated doses schedule. Seventy-six R/R B-NHLs (including 14 diffuse large B-cell lymphoma, DLBCL) were enrolled. Results showed that doses below 60 μg/m^2/day were associated with poor response rates while a dose of 90 μg/m^2/day was limited by neurotoxicity. In the extension phase, 11 patients with R/R DLBCL received the target dose with an overall response rate (ORR) of 55% and a complete remission (CR)/unconfirmed CR rate of 36%. With regards to adverse events (AEs), neurologic events occurred in 71% of patients with >20% of them reported grade 3, while no grade 4 or 5 events occurred[3].

Viardot et al. in a limited phase 2 study (21 evaluable patients) showed an ORR of 42% with a CR rate of 19%. Notably, grade 3 AEs were reported in 22 (95.7%) of patients with encephalopathy (9%) and aphasia (9%) being the most common neurologic ones. No patient had a grade 4 or grade 5 neurologic events and no cases of cytokine release syndrome (CRS) was reported[4].

Finally, a phase 2 study by Coyle et al. evaluated Blinatumomab as a second salvage in R/R DLBCL cases. In 41 patients, after 12 weeks of therapy, the ORR was 37% with a CR rate of 22%. A high rate of treatment discontinuation was reported, resulting in only 59% of patients receiving more than 80% of their intended dose[5].

2. Glofitamab

Glofitamab is a humanized mouse-derived IgG1-like T-cell engaging bsAb possessing a 2:1 structure with bivalency for CD20 (which improves affinity for CD20-expressing cells) and monovalency for CD3. The fragment crystallizable (Fc) structure is characterized by the absence of an Fc γ receptor and complement binding site, which influences its pharmacokinetic and pharmacodynamic properties. Bacac et al. in a preclinical study had shown its superior potency compared with other tested bsAbs[6], encouraging research in the field of bsAbs as a whole.

In a phase 1/1b trial Glofitamab was used as a single-agent in R/R B-NHLs. The monoclonal anti-CD20 Ab Obinutuzumab was administered before Glofitamab in order to prevent CRS by occupying surface CD20 Ags on lymphoma cells and depleting peripheral B-cells. Glofitamab was given as an intravenous infusion, in 14- or 21-day cycles for up to 12 cycles, and an escalating doses schedule of 0.6 to 25 mg was used. One hundred and seventy-one patients were enrolled with a median age of 64 years (range, 22–85). Aggressive NHLs (aNHLs) (DLBCL, transformed follicular lymphoma, tFL), primary mediastinal large B-cell lymphoma, PMBCL, mantle cell lymphoma, MCL, and Richter's transformation) and indolent NHLs (iNHLs) (grade 1–3A FL) were enrolled; patients had a median of 3 prior lines of therapy (range, 1–13) and 90.6% were refractory to all prior therapy. Clinical activity was observed at all doses. Among patients with aNHLs, ORR

and CR rates were 48.0% and 33.1% respectively, including 41.1% and 28.8% in patients with DLBCL and 55.2% and 34.5% in patients with tFL. In grade 1-3A FL, 70.5% achieved response with a high rate of CR (47.7%). In an aNHL setting, the median duration of response (DOR) was 5.5 months (95% CI, 4.4 to not estimable; range, 0.8–28.8 months) and the median progression free survival (PFS) was 2.9 months (95% CI, 2.1 to 3.9). In grade 1–3A FL, the median DOR was 10.8 months (95% CI, 3.8 to not estimable) and the median PFS was 11.8 months (95% CI, 6.3 to 24.2). AEs were reported in 98.2% of patients, with the most common being CRS, occurring in 50.3% of patients at grade 1 and in 1.2% at grade 4. Symptoms of immune effector cell-associated neurotoxicity syndrome (ICANS) during CRS were uncommon and all resolved within 3–72 hours. Incidence of CRS increased with dose but declined considerably after the first administration. Grade ≥ 3 neutropenia occurred in 25.1% of patients and infections and febrile neutropenia occurred in 51.5% and 2.9% of patients, respectively[7].

These pieces of data were confirmed by another trial. Interim data presented the results of 52 patients with R/R NHLs who received Glofitamab step-up dosing with Obinutuzumab pretreatment to reduce toxicity. Glofitamab was administered intravenously in a weekly step-up dosing regimen with a schedule of either 2.5/10/16 mg or 2.5/10/30 mg. Glofitamab was given every three weeks for up to 12 cycles. A total of 52 patients were treated in the two cohorts; these patients had a mean age of 68 years (range, 44–85) and 53.8% were male. More than half of the patients (53.8%) had aNHLs (DLBCL, tFL, Richter's transformation, MCL), while 46.2% of patients had indolent grade 1-3A FL. Patients were highly pretreated (median of 3 lines of therapy consisting of chemoimmunotherapy, autologous stem cell transplantation in 21.2%, a PI3K inhibitor in 9.6%, chimeric antigen receptor, CAR, T-cell therapy in 5.8%, and cancer immunotherapy in 1.9%). The ORR was 63.5% for all patients with a complete metabolic response (CMR) observed in 53.8% patients. In those with iNHLs the ORR was 66.7% and the CMR rate was 54.2%, versus 60.7% and 53.6%, respectively, in the aNHLs group. CRs were generally achieved early and observed from the first or second response assessment. Almost all patients (98.1%) experienced at least 1 AE, and 88.5% had treatment-related events. No fatal AEs were reported. The most common AEs were CRS, neutropenia, pyrexia, and thrombocytopenia[8].

Several trials are still ongoing, and results are pending.

3. Mosunetuzumab

Mosunetuzumab is a fully humanized bispecific IgG1 monoclonal Ab, binding CD20 on tumor cells and CD3 on T-cells. It too has a modified Fc with no Fc γ receptor or complement binding site, and it presents only one binding site to CD20. It is currently under study as monotherapy or combined with other drugs to treat B-cell NHLs.

The phase 1/1b GO29781 study (clinical trial information: NCT02500407) evaluated mosunetuzumab monotherapy in patients with aggressive and indolent R/R NHLs. Mosunetuzumab was given with a step-up dose on days 1, 8, and 15 of cycle 1, followed by a fixed dose on day 1 of each subsequent cycle up to a maximum of 17 cycles. The schedule ranged from a weekly step-up dose of 0.4/1/2.8 to 1/2/40.5 mg. Two hundred and seventy patients were evaluated (66.7% had an aNHL — including DLBCL, tfFL, and MCL— and 31.5% an iNHL). Of note, patients were heavily pretreated and 11.1% had received prior CAR T-cell therapy. Efficacy analysis showed high response rates in both aNHLs and iNHLs. Indeed, an ORR of 37.4% (CR rate 19.5%) and 62.7% (CR rate 43.3%) was reported in aNHLs and iNHLs respectively. In CAR T-cell R/R patients the ORR was 38.9% (CR rate of 22.2%)[9].

Similarly high response rates were reported in the population of the POD24 trial. In all groups, responses were durable over months with a median DOR of 20.4 months (95% CI: 9.4–22.7). AEs were reported in 60 patients (97%); 14 (23%) experienced CRS. CRS occurrences were reversible, mostly of grade < 2 and predominantly during the first cycle. No patient required tocilizumab, intensive care unit admission or use of vasopressors for CRS management. Neurologic AEs were observed in 28 patients (45%) with headache (24%), insomnia (15%), and dizziness (11%) the most reported. No grade ≥ 3 neurologic AEs were reported[10]. These safety data wereconfirmed in a heavily pre-treated, R/R CAR-T cell therapies population[9].

A subcutaneous monotherapy with Mosunetuzumab was tested in study GO29781 (clinical trial information: NCT02500407) to investigate alternative dosing strategies. R/R patients with aNHLs or iNHLs were included, and doses of 1.6 to 20 mg once every three weeks were considered. High efficacy rates were reported, with an ORR of 86% and a CR rate of 29% in patients with iNHLs and 60% and 20% in patients with aNHLs, respectively. All responses were durable with a median of 6.9 months. The subcutaneous administration of Mosunetuzumab has shown a low absorption rate and a high bioavailability (>75%) with a favorable toxicity profile compared to the intravenous formulation (reduced rate of grade ≥ 2 CRS at doses below 13.5 mg)[11].

Mosunetuzumab has also been assessed in the first-line setting, as monotherapy or in association with chemotherapy. In the phase 1/2 study GO40554 (clinical trial information: NCT03677154), Mosunetuzumab monotherapy is being evaluated in patients 80 years of age or older or in patients with untreated DLBCL aged 60–79 years who are ineligible for R-CHOP chemotherapy. Of the 19 evaluable patients, eight patients received the weekly step-up dose of 1/2/13.5 mg while 11 patients received the 1/2/30 mg dose. Treatment was continued for up to a maximum of 17 cycles. The median age was 84 (range: 67–100) years. The ORR was 58% and the CR rate was 42%[12].

Similar efficacy data were shown by the phase 1b/2 GO40515 trial (clinical trial information: NCT03677141), in which Mosunetuzumab was evaluated in R/R NHL patients and also in early-stage DLBCL, CHOP chemotherapy eligible patients. Mosunetuzumab was administered in a weekly step-up dosing regimen at 1/2/13.5 mg or 1/2/30 mg doses in R/R NHL. In the seven patients with R/R NHL, the ORR was 86% with a CR rate of 71%. In the 27 evaluable DLBCL patients, the ORR was 96% and the CR rate was 85%. Grade ≥ 3 AEs occurred in 37 patients (86%), with nineteen patients (53%) with previously untreated DLBCL having mild CRS events, while no ICANS events were observed [13].

4. Odronextamab

Odronextamab (REGN1979) is a fully human IgG4-based bsAb binding CD20 and CD3, which has been evaluated in the NHLs R/R setting. In a phase 1 study (clinical trial information: NCT02290951), odronextamab was administered in a step-up dosing regimen over three weeks followed by a fixed weekly dose until week 12. After this, maintenance dosing was given. Preliminary data is available for 127 patients with R/R NHLs with doses ranging from 0.03 to 320 mg. This cohort included a heavily pre-treated group of patients with DLBCL, grade 1–3a FL and MCL, with 29 patients having received prior CAR T-cell therapy. In patients with R/R grade 1–3a FL, odronextamab, at a dose of ≥ 5 mg, achieved an ORR of 92.9% and a CR rate of 75.0%. The median DOR was 7.7 months. In patients with DLBCL, excluding those who had received prior CAR T-cell therapy, in those treated at doses ≥ 80 mg (n = 10) the ORR and CR rate were both 60%. The median observed DOR in the DLBCL group was 10.3 months. In those DLBCL patients who relapsed after CAR T-cell therapy, 21 patients were treated at doses ≥ 80 mg, with an ORR of 33.3% and a CR rate of 23.8%. Grade > 3 CRS occurred in 9 patients (7.1%) during the first two weeks of step-up dosing and resolved within a median of two days (range 1–41) with supportive care measures. No patient discontinued Odronextamab due to CRS. Grade 3 neurologic AEs were noted in 3 (2.3%) patients. None of these events required treatment discontinuation. No grade 4 or higher neurologic AEs were reported [14].

5. Epcoritamab

Epcoritamab is a IgG1 bsAb which binds CD20 and CD3 and is administered via subcutaneous injections. In a phase 1/2 study (clinical trial information: NCT03625037), patients with R/R NHLs received a subcutaneous injection of Epcoritamab at a fixed weekly dose for two 28-day cycles, fortnightly for four cycles, and every four weeks thereafter. Preliminary data presented results for 67 patients (67% with DLBCL, 18% with FL, and 6% with MCL) with an ORR of 66.7% (CR rate of 33.3%) for doses > 12 mg. Notably, of 9% who had received previous CAR T-cell therapy, all responded (two patients achieving a CR and the other two a partial response). Of the seven patients with DLBCL who received a dose ≥ 48 mg, the ORR was 100% (28.6% CRs). High efficacy was also shown in FL patients who received a dose ≥ 0.76 mg with an ORR of 100% (two patients achieved a CR). In the four patients with MCL, responses were observed in two patients with blastoid variant MCL. Data on the duration of response are not yet available. CRS events were all grade 1/2 (58%) with no grade 3/4 events, and limited neurotoxicity was observed (6%, all transient, with 3% at grade 1 and 3% at grade 3). There were no dose-limiting toxicities[15].

6. Novel Perspective and bsAbs in Clinical Development

Although bsAbs hold great promise, it is still challenging to achieve high clinical performance and reduced side effects; in addition, the research for new immunological targets and pathways is very active.

For instance, ROR1, a a receptor tyrosine kinase uniformly expressed on the cell surface of malignant B cells, carcinoma, sarcoma, and melanoma, is a highly attractive candidate for targeted cancer therapy. NVG-111 is a humanized, tandem singel chain fragment variable bsAb binding ROR1 and CD3 which has been shown to be a potent tumor cell killer in vitro. In vivo, it has also been shown to engage a membrane epitope in the Wnt5a-binding frizzled domain, proximal to ROR1, and to thus redirect T-cell activity. In an ongoing phase 1/2 study in patients with R/R chronic lymphocytic leukemia (CLL) and MC, an escalated doses schedule of 0.3 to 360 µg/day is being evaluated; it is being administered via a continuous infusion over three cycles, each consisting of 21 days of treatment and 7 days without treatment. Patients are on their

second or further line of therapy after a Bruton's tyrosine kinase inhibitor, or venetoclax (clinical trial information: 2020-000820-20). Results are pending [16].

CD22 is another attractive target for B-cell malignancies due to its strong expression on the cell surface of B-cells. Several CD22-targeting monoclonal Abs, Ab-drug conjugates, radioimmunoconjugates, CAR T-cells, and bsAbs are under investigation. JNJ-75348780, a bsAb targeting CD3 and CD22 in patients with R/R NHLs, including CLL, is currently undergoing a phase 1 trial (clinical trial information: NCT04540796), but preliminary results have not yet been published[17].

Immune checkpoint inhibitors have shown high clinical activity in many tumor types; however, only a fraction of patients benefit. In a preclinical setting, combining CD137 agonists with these inhibitors increased antitumor activity, but attempts to translate these observations into a clinical setting were hampered by systemic toxicity. A bispecific human CD137x programmed death ligand 1 (PD-L1) Ab, MCLA-145, potently activated T-cells and enhanced T-cell priming, differentiation, and memory recall responses. In vivo, the antitumor activity of MCLA-145 was superior to immune checkpoint inhibitor comparators and was related to intra-tumor recruitment and expansion of CD8+ T-cells. No graft-versus-host disease was detected, unlike other Abs that inhibit the programmed death (PD)-1 and PD-L1 pathways. MCLA-145 is currently being evaluated in an open label, single-agent dose-escalation study with expansion cohorts for confirmation of dose/safety and preliminary efficacy in advanced or metastatic malignancies (clinical trial information: NCT03922204)[18][19].

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