Talquetamab ----------

Now I'll introduce Talquetamab, a recently approved bispecific antibody for relapsed or refractory multiple myeloma (RRMM). Talquetamab targets GPRC5D, a protein highly expressed on myeloma cells, and CD3, which is found on T cells. This bispecific antibody binds both GPRC5D and CD3, bringing T cells in close proximity to the cancer cells.

As a result, it redirects T cells to kill myeloma cells by releasing perforin and granzymes, as shown in the diagram. Importantly, this process is MHC-independent, meaning Talquetamab can activate T cells even when tumor antigen presentation is poor.

Overall, Talquetamab offers a novel strategy to target MM, especially for patients who have failed multiple lines of prior therapy.

Talquetamab 2----------

This figure summarizes the clinical response rates observed in the trial, where Talquetamab was tested at various dosing regimens, both subcutaneous (SC) and intravenous (IV).

The patients in this study were heavily pretreated, with most having received at least three or more prior lines of therapy, including proteasome inhibitors, IMiDs, and anti-CD38 antibodies.

As shown here, Talquetamab achieved overall response rates between 64% and 72%, depending on dose and schedule.

More than half of the patients reached at least a very good partial response (VGPR), and a substantial number achieved stringent complete responses, which indicate deep and sustained remission.

These results are remarkable considering the difficult-to-treat nature of RRMM, and they demonstrate dose-dependent, durable clinical activity across multiple regimens.

In summary, this data highlights Talquetamab's strong potential as a powerful and flexible therapeutic option in multiple myeloma.

[KA]

Another current research focus is trispecific antibodies.

As the name suggests, trispecific antibodies have 3 binding sites so they can bind to one more thing than bispecific antibodies, so they're like the next step up for this technology. This also means they can have exponentially more formats, as you can see from the figure.

Trispecific antibodies can be made from fusing parts of existing antibodies via flexible linkers, heterodimerisation, knob-in-hole mechanisms, or other methods. Since each of the building parts is completely modular, this gives us a lot of freedom in terms of the functionality of the antibody.

Now, the reason I brought up trispecific antibodies is that, remarkably, they manage to address a lot of the major challenges faced by antibody cancer treatments.

The first major challenge is called antigen escape. This is where the cancer cells experience antigen loss due to the selective pressure, which makes them even more stealthy than they already are. This, as you can imagine, drastically reduces the effectiveness of the treatment.

There is a common trispecific antibody design with one site recruiting T cells and the other two targeting a tumour-associated antigen (TAA). With dual-TAA targeting, tumour escape can be reduced dramatically.

One study even showed the chance of relapse dropped to zero, which indicated that the antibody can effectively aid in tumour eradication.

Another challenge would be the short plasma half-life of antibodies since they are very small and are readily filtered by the kidneys. With trispecific antibodies, one of the arms can be dedicated to binding to a common large plasma protein called albumin, which increases the plasma half-life of the antibodies from 2 hours to up to 3 weeks.

Next up, the working principle of bispecific antibodies is to activate the immune system via target clustering. However, the continuous use of antibody treatment can lead to the production of anti-drug antibodies, which causes unintended clustering of the antibody drug, leading to off-target activation and thus toxicity.

While trispecific antibodies also have this problem, they have also been shown to be effective at much lower concentrations than bispecific antibodies, which greatly reduces immunogenicity and undesirable toxicity.

When combined with the longer half-life, this can also produce longer-lasting tumour suppression effects.

Despite these advances, however, the problems of manufacturing complexity and stability concerns remain to be tackled.

As previously described for BsAb, TsAb can be divided in IgG-like formats (with a Fc region) and non-IgG-like formats, (without a Fc region), according to their similarity with the conventional IgG structure (Figure 1). Non IgG-like formats consists of antibody-derived building blocks fused via flexible linkers, the simplest arrangement being 'beads-on-string'. From higher to smaller molecular weight, these binding domains can be antigen-binding fragments (Fab), single-chain variable fragments (scFv) or single domain antibodies (sdAb).

1 Manufacturing?

a CD19/CD22/CD3 TsAb was designed by fusing anti-CD19 scFv and anti-CD22 sdAb to a CD3 binding Fab

The format for the trispecific antibody was developed by integrating the previously described CODV-Ig bispecific antibody prototype 19 with a conventional antibody arm by heterodimerization using knob-in-hole 64 mutations in the CH3 domain of the IgG1 and IgG4 Fc region, as described previously 13 . For CODV bispecific antibody design, two binding domains from any given antibodies can be linked together through various linkers in inversed order for light chains and heavy chains. More specifically, monoclonal antibodies targeting CD38 (CD38 VH1), CD28 (CD28 sup) and CD3 (CD3 mid) were tested for possible combinations including each antibody position and linker type. The combinations with the best ability retaining the enzyme-linked immunosorbent assay binding and T cell activation and good manufacturability were used for trispecific antibody development

2 Application:

The main application field of TsAb remains oncology, with at least one of the three specificities intended to bind T or NK cells, and at least one targeting a tumour-associated antigen (TAA) in most designs. The two distal binding domains recognize different TAA, while the central domain recruits effector T cells.

2.1 More vigilant:

The incorporation of a second in-cis binding antibody moiety targeting a different TAA expressed on the same tumor cells offers additional advantages. For example, dual TAA-

targeting may contribute to prevent tumor escape by antigen loss caused by selective pressure in comparison to conventional single TAA-targeting TCE and may help to overcome antigenic heterogeneity.

2.2 Fewer relapse:

In this case, the TsAb was superior inducing T-cell specific cytotoxicity and cytokine production in vitro against CD19+ and/or CD22+ tumor cells and demonstrated significantly enhanced antitumor efficacy in a patient-derived xenograft (PDX) model of B-ALL, compared with the corresponding BsAb alone or in combination. Remarkably, leukemia relapse was observed in all animals, independently of the initial response, except in the group treated with the TsAb.

2.3 Longer-lasting effect:

The resulting TsAb induced not only a more durable growth inhibition of double-positive tumors compared with the combination of corresponding BsAb, but also overcame tumor heterogeneity and elicited tumor regression in mice coimplanted with HER2+ or VEGFR2+ tumors in each flank.

2.4 Lower concentrations:

The use of CD28 agonists is associated to the risk of severe side effects due to cytokine release since the 2006 TeGenero clinical trial [73]. Importantly, maximum MM cell killing in vitro was observed at CD38/CD3/CD28 TsAb concentrations far below serum levels well tolerated in non-human primates (NHP). The authors argue that monovalent CD28 binding by the TsAb is less prone to induce cytokine release than the bivalent anti-CD28 IgG used in the above-mentioned trial.

2.5 Longer half-life:

A third subtype of trispecific TCE comprises binding domains against a single TAA and a single T-cell activating receptor, along with a moiety for increased serum half-life.

In fact, the 55-kDa BiTE blinatumomab has a serum half-life of only 2 hours and, therefore, continuous intravenous infusion is required [75]. The inclusion of albumin-binding sdAb is a widely used half-life extension strategy for small biotherapeutics. Albumin has a serum half-life of 3 weeks because of its size and FcRn-mediated recycling, properties shared with canonical IgG antibodies [76]. The great advantage of extended serum persistence is a more even drug concentration, less frequent dosing, and the potential to decrease doses without compromising therapeutical efficacy.

Challenge 3 (immuno) ----------

In this scenario, the bispecific antibody is designed to activate the immune system by clustering target A when bound to target B — for example, stimulating two receptors on a tumor cell.

However, anti-drug antibodies, or ADAs, may bind to the drug and cross-link it like a bridge. This can lead to unintended clustering of target A alone, even without target B.

As a result, the immune system may be activated in a non-specific way, potentially causing systemic toxicity.

Conclusion----------

Summary

Bispecific antibodies offer the ability to simultaneously target two distinct antigens, achieving therapeutic effects that are difficult to obtain with monoclonal antibodies alone. They hold great potential for applications in oncology, autoimmune diseases, and infectious diseases, with multiple BsAbs already approved and in clinical use.

Future Perspective

BsAb research continues to evolve, with the development of more potent, stable, and versatile formats, including multispecific antibodies and novel combination strategies, driving innovation in next-generation therapeutics.---