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New Drugs

Bispecific antibodies in haematological malignancies

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ABSTRACT

Bispecific antibodies (bsAbs) combine the binding sites of two monoclonal antibodies in one molecule. The close proximity of a tumor specific antigen and an effector cell antigen results in a targeted activation of effector cells. The mechanism is similar to the chimeric antigen receptor (CAR) T-cells, recently approved in two haematologic cancers. CAR T-cells and bsAb represent the most powerful tools for major-histocompatibility complex (MHC) independent T-cell immune response against cancer. In contrast to CAR T-cells, bsAbs are "off the shelf" drugs. As a drawback, the efficacy is dependent on a prolonged application. More than 40 years of intensive research generate a plethora of bispecific constructs with a remarkable difference in manufacturability, stability, half-life time and receptor affinity. Blinatumomab was the first approved bsAb in relapsed and refractory acute lymphoblastic leukemia. By the mature experience of blinatumomab in more than 10 clinical trials over more than one decade, we learned some lessons on how to use this new principle. The efficacy is higher in patients with less tumor burden, suggesting the use as consolidation more than for initial debulking. Main resistance mechanisms are extramedullary relapses and the expression of the inhibitory PD-L1 molecule, suggesting the value of combination with checkpoint inhibitors. CD19 loss is infrequent after blinatumomab, preserving the option for alternative CD19-direct treatments. New bsAbs in lymphoma, myeloma and acute myeloid leukemia enter phase-I trials, together with many new constructs in solid cancer.

Historical perspective

In the early 60s, Alfred Nisonoff – a pioneer in antibody engineering – worked, for the first time, on the idea of "preparing antibodies of mixed specifity" [1]. However, it took more than 20 years, along with the introduction of the hybridoma technique, to establish the first monoclonal bsAb, enabling T-cell recruitment by Staerz and Bevan in 1985 [2]. This discovery was the origin of a rapidly growing interest in these technologies, between 1985 and 1995, called the "bispecific explosion" [3]. At the end of the nineties, there was a plethora of different bsAb constructs. The first clinical trial in humans was performed in 1990 [4] using a coupled antibody with specificity to T-cell-receptor and glioma antigen in glioblastoma patients. The first bsAb in haematologic malignancies might be a clinical trial using a CD19 × CD3 antibody in Non-Hodgkin-lymphoma (NHL) in 1995 [5]. This antibody showed no clinical response, but the tumor necrosis factor alpha associated cytokine release syndrome (CRS) was recognized as a relevant side effect. In 1997, a Natural Killer (NK)-cell activating CD30x CD16 antibody shows some clinical responses in Hodgkin lymphoma [6]. In 1995, preclinical data of the first bispecific T-cell engager (BITE™) against CD3 and 17-1A was published [7], which was the ancestor of the CD19 × CD3 BITE blinatumomab [8].

In 2001, Blinatumomab entered a first-in-man study [9] in Germany and Sweden, based on short-term intravenous infusions at doses ranging from 0.75 to 13 μg/m [2]. These trials were terminated early due to the lack of clinical response and the occurrence of neurologic adverse events, cytokine release syndromes (CRS) and infections. In 2004, a phase-I dose escalation trial began with a continuous infusion, resulting in the first meaningful clinical responses at a dosage of 15 $\mu g/m^2$/day [10]. The observation of depletion of CD19 positive peripheral blood cells and the clearance of bone marrow at very low dose levels was the rationale for the use in leukemic disease. Between 2006 and 2008, heavily pretreated pediatric patients with acute lymphoblastic leukemia (ALL) received blinatumomab as a compassionate use program and showed responses [11]. These observations justified the further clinical development in ALL.

Ten years later, Blinatumomab was approved by the FDA and FMA for the treatment of relapsed and refractory B-cell precursor ALL. The FDA accelerated approval in 2014 was converted in a full approval in July 2017, including patients with Philadelphia-positive and pediatric ALL. Blinatumomab was not the first approved bsAb. In 2009, the trifunctional EPCAM × CD3 antibody Catumaxomab was approved by

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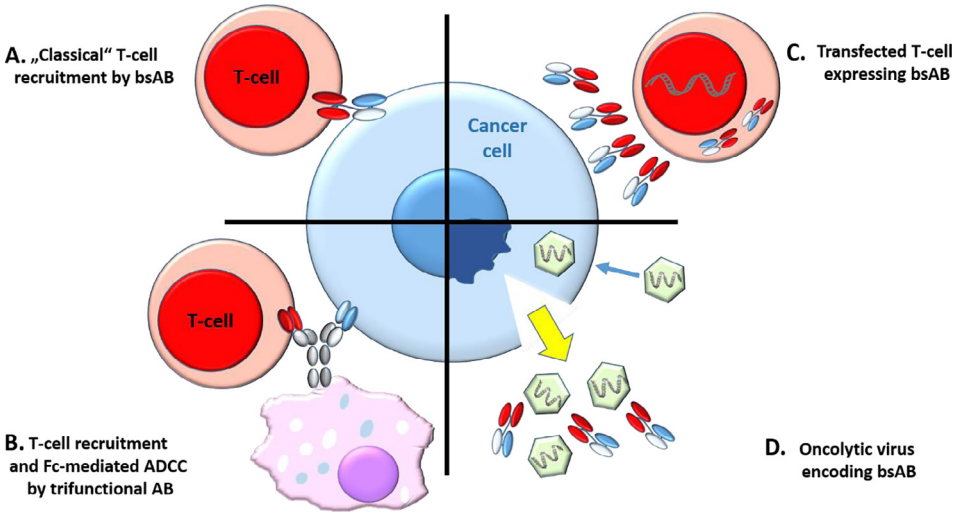

Fig. 1. Mode of action of bispecific antibodies and novel constructs (bsAb: bispecific antibodies; ADCC: antibody dependent cellular toxicity).

EMA for the local treatment of malignant ascites in solid tumors. However, the marketing authorization of Catumaxomab was withdrawn in July 2017 at the request of the manufacturer. Due to the success of blinatumomab and the recent developments in antibody engineering, there is a growing interest in bsAbs and novel construct possibly heralding a second “bispecific explosion” in the next years (see Fig. 1).

Terminology

More than 30 years of development result in a pronounced diversity of different bispecific molecules in clinical and preclinical trials. In a recent review, there is an overview about the “zoo” of more than 100 bispecific constructs [12–14]. Most of them combine two or more variable regions of monoclonal antibodies in complexly engineered molecules - with differences in size, half-life, stability and receptor affinity. The first generation of bsAbs was chemically coupled. Most of the more recent developed antibodies are based on recombinant DNA technology.

A striking difference between bsAbs is the size of the molecule, which depends on the presence of the Fc part of a monoclonal antibody. Variable domain-only antibodies like BiTE™ (bispecific T-cell engager), DART™ (Dual-Affinity Re-Targeting) or TandAb™ (Tandem Antibodies) have short half-lives as they lack the Fc domain. For example, the molecular weight of blinatumomab is only 50 kDa resulting in a half-life of less than two hours. A major drawback, particularly in BITEs, is the need of a continuous infusion to maintain exposure. Full-size bsAb have a near-native antibody architecture including the Fc part, which enables comfortable dosing intervals. The Fc part of monoclonal antibodies can hinder the formation of the cytolytic synapsis by attracting macrophages. Therefore, the Fc function is mitigated by mutated Fc binding sites in some of the new constructs.

BsAbs have *per definitionem* two different specificities including two different variable regions of monoclonal antibodies. Constructs of tri- or multispecific antibodies (e.g. triabodies) combine more binding sites. BsAbs can be bi-, tri- or even tetravalent, if it has more than one binding site of one specificity per molecule to augment the binding capacity. BsAbs with a functioning Fc part, which can attract macrophages, are called “trifunctional” (e.g. Catumaxomab). An overview about this terminology is in Fig. 2.

In cancer, the most prominent function of bsAb is the recruitment of immunocompetent cells for redirected tumor lysis. The majority of bsAbs binds to the CD3/T-cell receptor complex to recruit T-cells. However, there are alternative constructs binding CD16 (NK-cells), CD64 (monocytes and macrophages) and CD89 (granulocytes). BsAbs

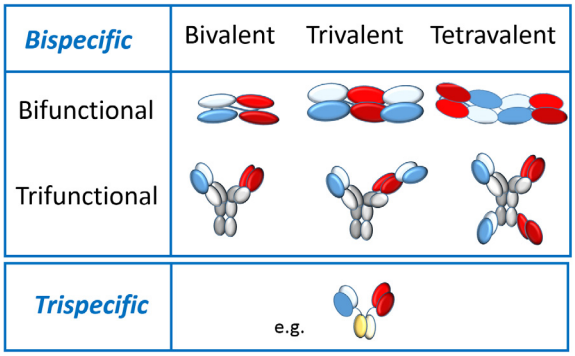

Fig. 2. Nomenclature of bi- or multispecific antibody constructs.

can also neutralize or activate receptors or their ligands (e.g. Crossmabs, DVD Ig). These constructs can be applied to cancer, but also to inflammatory or autoimmune disease (review in [15]). BsAbs can force the association of proteins or enzymes, which is the principle of emizicumab, recently approved by the FDA for the treatment of hemophilia A with acquired inhibitors.

Additional differences and characteristics of the “zoo” of bispecifics are explained by the challenge in manufacturing, e.g. to prevent the mispairing of heavy or light chains. There are several excellent technical reviews on this issue [12–16].

Blinatumomab

Blinatumomab is the first FDA and EMA approved bispecific construct for the treatment of relapsed and refractory (r/r) ALL. It is a small (55 kDa) single chain peptide connecting two variable antibody fragments directed against CD3 and CD19 [10]. Blinatumomab induces the formation of a cytolytic synapsis and activates T-cells without costimulatory molecules. There is a continuous recharging of granzymes resulting in a continuous attack of tumor cells without anergy or T-cell apoptosis [17]. Blinatumomab leads to an expansion of CD8 positive T-cells, dominated by cytotoxic CD8+ T effector memory (TEM) [18].

A major drawback is the short half-life requiring a continuous intravenous infusion and a port system over several weeks. Patients with ALL receive up to 5 cycles of a 4-week infusion with an intermission of two weeks. Patients with Non-Hodgkin lymphoma (NHL) were treated in clinical trials over 8 weeks, followed by an additional cycle of 4 weeks in responding patients. On the other hand, the short half-life may have some advantages. Severe side effects are manageable by