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Double hit — bispecific antibodies in cancer therapy

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ABSTRACT

Immunotherapy has emerged as a promising strategy for cancer treatment, with bispecific antibodies (BsAbs) demonstrating significant therapeutic potential. BsAbs are biological molecules capable of simultaneously binding to two distinct antigens, allowing the immune response to target cancer cells precisely. However, despite promising results in preclinical studies and early clinical trials, immunotherapy based on these antibodies faces several significant issues that require careful consideration. One of them is the development of therapy resistance, which often leads to a loss of treatment effectiveness. Another challenge is the associated toxicity of immunotherapy. While BsAbs are designed to limit adverse effects, there remains a risk of side effects that can impact the quality of life for patients. Furthermore, it should be noted that the production of BsAbs is burdened with significant costs and involves complex processes, negatively affecting the accessibility of this therapy for the majority of patients. Hence, continuous efforts are necessary to develop more efficient and cost-effective methods for producing these antibodies to enable a broader range of patients to benefit from this innovative therapy.

Keywords: bispecific antibodies, methods of antibody design, immunotherapy, adverse effects

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Introduction

Groundbreaking discoveries in the field of anti-cancer therapy using multifunctional synthetic biotherapeutics have significantly influenced the development of cancer immunotherapy and research into new antibody interaction strategies [1]. Traditional targeted therapies and immunotherapeutic agents typically are focused on a specific therapeutic target. However, thanks to remarkable achievements in antibody engineering, various innovative constructs, such as bispecific antibodies (BsAbs), have been created [2]. The basic structure of an antibody is shown in Figure 1.

Bispecific antibodies are generated through such techniques as chemical conjugation or genetic recombination and exhibit specific structures, compositions, and functional, biochemical, and pharmacological properties [3, 4]. As a result, they exert effector functions that go beyond natural functions of antibodies, with applications spanning diagnostics, imaging, prophylaxis, and therapy [4]. Initially, their action primarily focused on redirecting effector cells for anti-cancer therapy. However, over the last decade, numerous therapeutic strategies based on BsAbs have been developed, including retargeting cells, effector molecule delivery, and genetic payload carriers, along with investigations into pre-targeting, dual targeting, overcoming biological barriers, and extending half-life [5–7]. These antibodies are considered potential methods of treatment in other indications, including cancer, autoimmune diseases, chronic inflammatory conditions, and neurodegeneration [8].

Currently, research is underway on numerous BsAb projects, with over a hundred in clinical evaluation for cancer treatment. However, the majority of these projects are still in the early stages of clinical trials, and only four bispecific antibodies have received approval from

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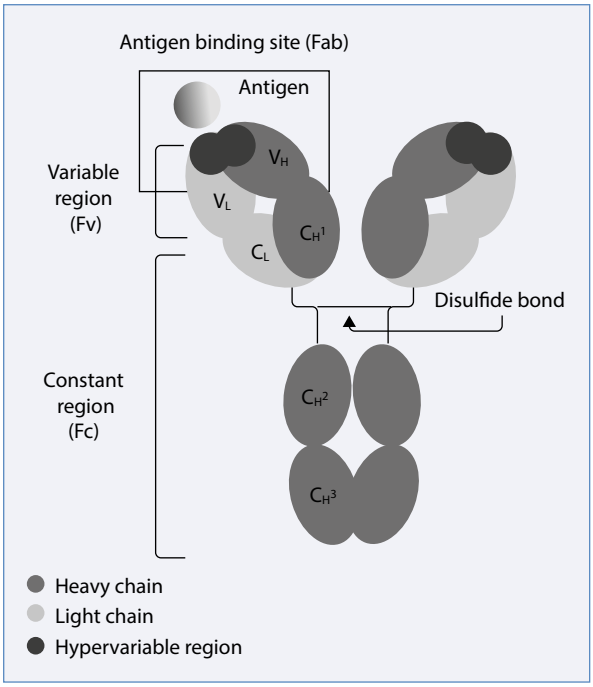

Figure 1. Basic structure of an antibody

the Food and Drug Administration (FDA) for clinical use [9, 10]. In these studies, mechanisms of BsAb action are being analyzed, enabling targeted recognition of various cancer-related targets, such as cell proliferation control, angiogenesis inhibition, prevention of invasion, and modulation of the immune system [11, 12]. Nevertheless, the implementation of immunotherapy is not without potential side effects, limiting its application. Therefore, further research is needed to refine these therapies and minimize undesirable effects [13].

Various methods of antibody design

Recombinant antibodies have been used for therapeutic purposes for approximately 35 years, and currently, many new ones are being discovered. Since the advent of recombinant antibody technology, there has been a significant increase in interest in their production and application, as they possess new mechanisms of action that are typically not achievable with conventional monospecific antibodies. Their structural diversity can be achieved through chemical recombination, DNA recombination, as well as CrossMab technology [14, 15].

Chemical recombination and DNA recombination are the two main methods for producing bispecific antibodies, which have significantly contributed to advances in anticancer and autoimmune therapies. The first method was introduced in the 1980s and allows for the creation of BsAbs by modifying their fragments using bifunctional reagents. One variation of this technique is the CovX-Body technology, which greatly extends the half-life of low molecular weight drugs, enabling less frequent administration of BsAbs (Fig. 2A). Meanwhile, the second method, developed in the 1990s, enables controlled production of chimeric or humanized antibodies using genetic engineering techniques, including "knobs-into-holes" (KiH) (Fig 2B) [13, 16–28]. The difference between different antibody types is shown in Figure 3. However, these methods have certain drawbacks, such as high costs, risk of adverse effects, and ethical issues that require strict control and regulation [14, 29].

In recent years, the CrossMab technology has become increasingly popular, enabling the correct pairing of light and heavy antibody chains (Fig. 2C) [30, 31]. This method offers advantages in terms of stability, production, and versatility compared to other techniques. However, research is still ongoing to optimize the manufacturing and quality control of BsAbs obtained using this method [15, 32–34].

Description of selected antibodies and their applications

Bispecific antibodies were first described in the 1960s, and since then, our knowledge about them has significantly expanded, as evidenced by the growing number of studies dedicated to BsAbs, which has notably risen over the past 10 years. The particular interest in these antibodies stems from their therapeutic applications. In the last decade, 14 bispecific antibodies have been approved for therapeutic use: 11 for cancer treatment and 3 for non-oncological indications [13, 35].

Catumaxomab

One of the early representatives of BsAbs is catumaxomab, which was approved by the European Medicines Agency in 2009. However, it has not been produced and available for use in Europe since 2017 [36].

The use of this drug in the therapy of cancerous ascites proves effective because there is no barrier for T lymphocytes or BsAb molecules to penetrate the peritoneum. Cancerous ascites consist of individual cells floating in fluid. The anticancer action of catumaxomab stems from its ability to bind both epithelial cells using the epithelial cell adhesion molecule (EpCAM) and T cells through CD3 (Fig. 4) [37, 38]. Therefore, this medication enhances the activation of the patient's immune system. It was administered intraperitoneally in small doses ranging from 10 to 100 mg four to five times at approximately 2-week intervals. One of the side

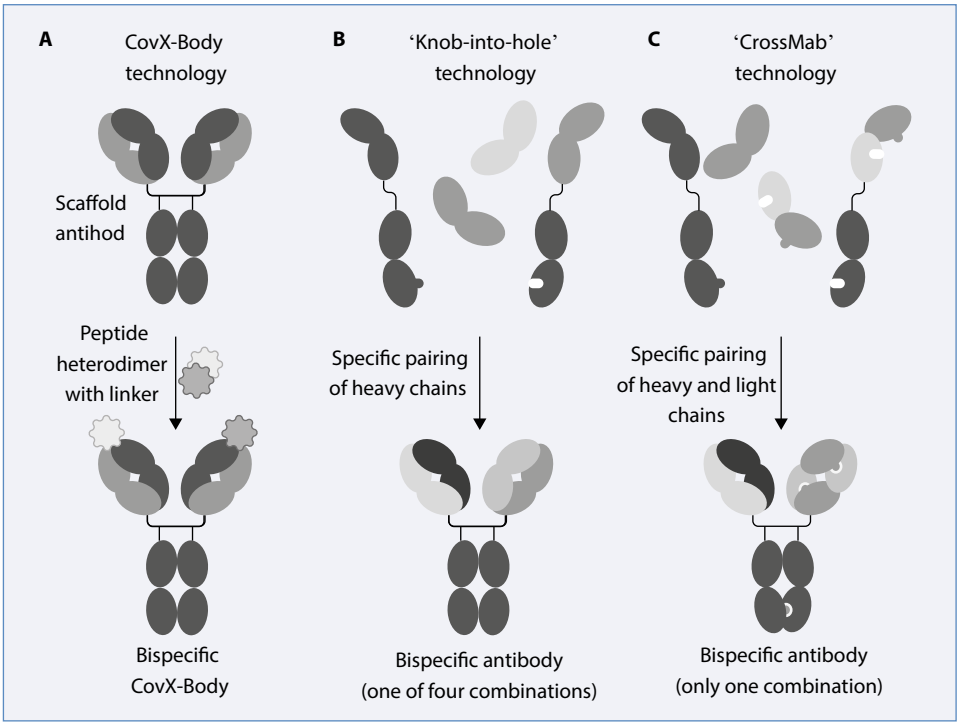

Figure 2. Chosen methods of bispecific antibody design

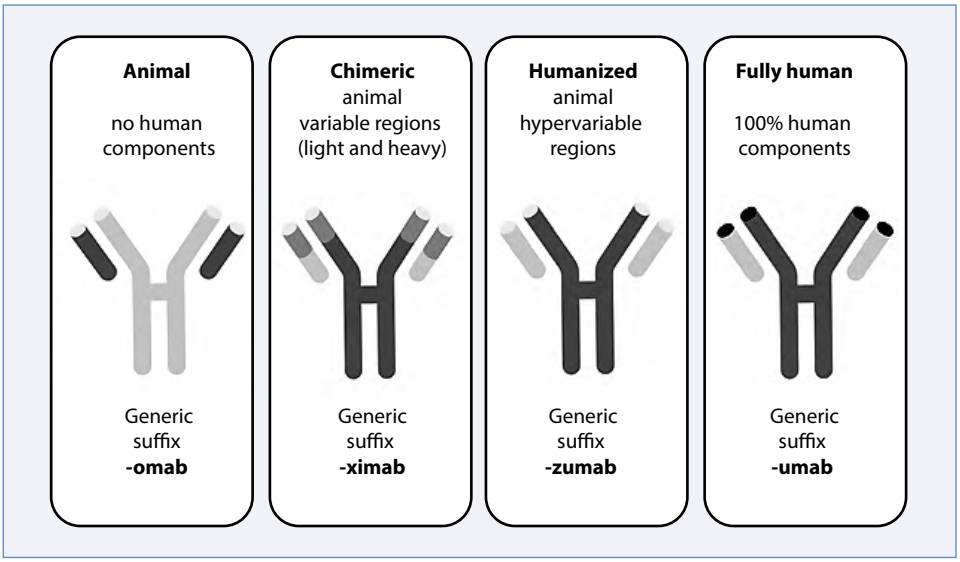

Figure 3. The evolution of monoclonal antibodies

effects of this therapy was the development of antibodies against mouse and rat Abs [39–41].

Blinatumomab

The second drug representing BsAbs is blinatumomab. Treatment with this antibody leads to a reduction in the number of B lymphocytes and their precursors in peripheral blood. After the completion of therapy, these cells gradually recover. Its efficacy in the treatment of B-cell malignancies was first demonstrated in 2008 in patients with refractory non-Hodgkin lymphoma. In 2014, the U.S. FDA approved blinatumomab for the treatment of Philadelphia chromosome-negative acute lymphoblastic leukemia as a second-line therapy. In the EU, the drug was registered in 2015 [42–44].

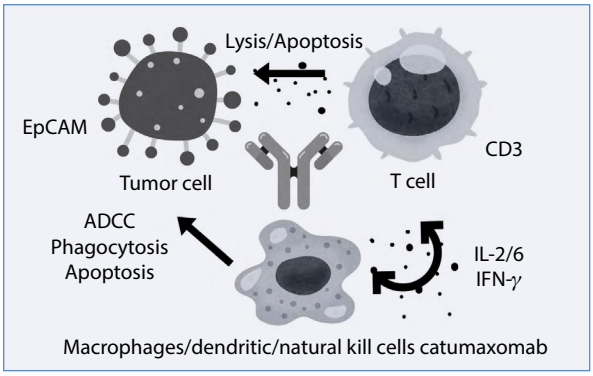

Figure 4. The mechanism of action of catumaxomab

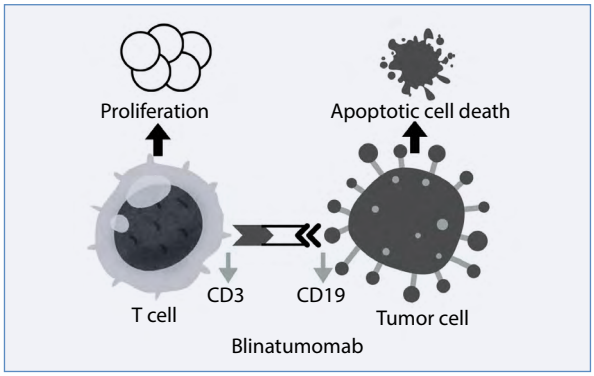

Figure 5. Mechanism of action of blinatumomab

The bispecific molecule of blinatumomab has two active targeting domains: one for the CD19 molecule present on the surface of B lymphocytes and the other for the CD3 receptor located on the surface of cytotoxic T lymphocytes (Fig. 5). Consequently, it directs primary CD3+ T lymphocytes against CD19+ lymphoma cells, providing cytotoxicity even at very low concentrations. It also induces an increase in the secretion of anti-inflammatory cytokines. The efficacy of treating patients with relapsed acute lymphoblastic leukemia was confirmed by remission obtained in 72% of patients [45–47].

This drug has a single-chain structure, enabling easy expression of the protein in significant quantities, giving it broad therapeutic potential. Unfortunately, this characteristic necessitates continuous intravenous administration of the drug as it is rapidly cleared from the bloodstream. The use of blinatumomab leads to a decrease in the number of B lymphocytes to below one cell/μl for 2 days, and they are nearly undetectable until the end of the therapy. In contrast to B cells, the number of T lymphocytes increases in all patients to a maximum level on day 1 and returns to normal within a few days. Moreover, within approximately 2 weeks, the number of T lymphocytes doubles in the majority of patients [48, 49].

Other approved bispecific antibodies

Among the registered immunoglobulins are amivantamab and tebentafusp. They demonstrate promising results and represent a significant advancement in combating locally advanced or metastatic non-small cell lung cancer (NSCLC) with exon 20 insertions in the *EGFR* gene after treatment with platinum-based chemotherapy, and uveal melanoma (UM) [50, 51].

Amivantamab is a bispecific IgG1 antibody with an active Fc region, consisting of two arms. One arm binds to the extracellular domain of EGFR, blocking the binding between the receptor and its ligand epidermal growth factor (EGF), while the other arm blocks the binding of the hepatocyte growth factor (HGF) ligand to the mesenchymal-epithelial transition factor (MET) receptor. This immunoglobulin leads to a reduction in the number of EGFR and MET receptors on the cell surface, both *in vitro* and *in vivo*. Additionally, amivantamab maintains its effectiveness even when binding to the EGFR or MET receptor alone. This results in the inhibition of protein signaling pathways, which hampers the growth and survival of cancer cells [52, 53]. It is noteworthy that in combination with chemotherapy (carboplatin-pemetrexed), with or without the addition of lazertinib, amivantamab significantly increases progression-free survival (PFS) compared to chemotherapy alone, reducing the risk of disease progression or death by 52% and 56%, respectively. However, in the case of a modified chemotherapy regimen using amivantamab and lazertinib longer monitoring is required [54].

Tebentafusp is an approved therapy for uveal melanoma. It is a fusion protein of modified T-cell receptors. It acts by binding to peptide-HLA complexes specific to CD3 on the surface of target cells, enabling redirection of T cells to gp100+ cells in the tumor. Tebentafusp induces recruitment and activation of various T cells, leading to cytokine secretion by them and promoting their migration from the bloodstream to the tumor. Studies have shown that this bispecific antibody is effective in treating uveal melanoma, with an overall survival (OS) rate of 73% in the tebentafusp-treated group compared to 59% in the control group after one year. The FDA has approved these BsAbs for use in adult patients who test positive for HLA-A*02:01 and suffer from unresectable or metastatic uveal melanoma [55, 56].

Investigational bispecific antibodies

The remarkably rapid progress in this field has resulted in numerous studies on bispecific antibodies. Currently, many BsAbs are being analyzed, and some

Table 1. Bispecific antibodies in clinical trials

Name	Target	Application	Clinical Trial Phase
Bintrafusp alfa	PD-L1, TGF-β	Non-small cell lung cancer	Phase 3
Erfonrilimab	PD-L1, CTLA-4	Non-small cell lung cancer	Phase 3
Linvoseltamab	BCMA, CD3	Multiple myeloma	Phase 3
Zanidatamab	HER2, HER2	Biliary tract cancer	Phase 3
KN046	PD-L1, CTLA-4	Triple-negative breast cancer	Phase 2
Plamotamab	CD20, CD3	Hematologic malignancy	Phase 2
Lorigerlimab (MGD019)	PD-1, CTLA-4	Advanced solid tumors	Phase 1
Tebotelimab	PD-1, LAG-3	Hematologic malignancy	Phase 1
Volrustomig (MEDI5752)	PD-1, CTLA-4	Advanced renal cell carcinoma, Non-small cell lung cancer	Phase 1

BCMA — B cell maturation antigen; CTLA-4 — cytotoxic T lymphocyte antigen 4; PD-1 — programmed cell death protein 1; PD-L1 — programmed death ligand 1; TGF-β — tumor growth factor beta receptor

of them are already in the final phase of clinical trials or have achieved registration. Examples of such antibodies include bintrafusp alfa, erfonrilimab, linvoseltamab, and zanidatamab [57–59].

Bintrafusp alfa is the first-in-class bifunctional fusion protein consisting of the extracellular domain of the human tumor growth factor beta receptor (TGF-βR) fused to a human monoclonal antibody of immunoglobulin G1 against programmed death ligand 1 (PD-L1). Consequently, this drug can simultaneously inhibit the PD-L1 and TGF-β pathways, aiding in the activation of the immune response against cancer cells. Bintrafusp alfa showed clinical activity and manageable safety in treatment of human papillomavirus (HPV)-associated cancers [57].

Erfonrilimab acts on the immune checkpoint proteins PD-L1 and cytotoxic T lymphocyte antigen 4 (CTLA-4), allowing it to modulate the immune response to cancer cells by enhancing the activity of T lymphocytes. Research is being conducted to evaluate the effectiveness, safety, and tolerance of erfonrilimab in combination with first-line chemotherapy for patients with non-small cell lung cancer [58].

Linvoseltamab is a bispecific antibody that engages T cells directed against B cell maturation antigen (BCMA) and CD3 and thus may be used to combat multiple myeloma. Currently, studies are underway to determine the optimal dose for patients with relapsed and refractory multiple myeloma (RRMM) who have undergone at least three previous lines of treatment [58].

Zanidatamab is an antibody that acts as an inhibitor by promoting antigen internalization and clearance and triggering antibody-dependent cell-mediated cytotoxicity (ADCC). It is designed against two epitopes of HER2. This BsAb demonstrates tolerance within the body and antitumor activity in patients with biliary tract cancer who are resistant to traditional treatment methods. This could provide significant clinical benefits, particularly due to its potentially favorable safety profile, which may be manageable in patients with this type of cancer [59, 60].

The Table 1 provides an overview of selected investigational bispecific antibodies used in anti-cancer therapy. It presents key information about these promising molecules, including their target, application, and clinical trial phase [57–65].

Evaluation of the immunogenicity risk in bispecific antibody therapy

One of the significant challenges in developing new biologic drugs with multifunctional domains is immunogenicity. Bispecific antibodies are genetically modified antibodies that combine different functional domains, allowing for targeting of two distinct cells. However, the fusion of diverse domains in a single drug may lead to the creation of novel formats, contributing to the exposure of cryptic epitopes or the formation of neoantigens triggering immunogenicity. Additionally, various factors related to the product, patient, or the complexity of conditions in anticancer BsAb studies can also influence immunogenicity. Therefore, the early assessment of immunogenic risk is crucial to enhance the chances of therapeutic success [4, 66–68].

Methods

The risk associated with using bispecific antibodies arises from the fact that these molecules contain a functional domain different from monoclonal antibodies (mAb). This domain includes sequences or structures resembling their endogenous counterparts, such as cytokines or hormones, which may contribute to the formation of neutralizing antibodies. These antibodies cross-react with the endogenous proteins, leading to a deficiency or disruption of their function. To address these challenges, tools for assessing immunogenic risk,

such as *in silico* algorithms and *in vitro* T-cell-based assays, have been implemented [69].

The use of *in silico* algorithms aims to determine the primary ability of the therapeutic protein's amino acid sequence to bind to the major histocompatibility complex class II (MHC II). However, this method tends to exhibit overpredictability. Therefore, one should not expect a direct correlation between *in silico* results and clinical immunogenicity [70].

Another tool for estimating this risk is the *in vitro* T-cell assay. This method relies on sequencing, evaluating the magnitude and speed of T-cell responses to the therapeutic protein. Typically, this analysis is performed on peripheral blood mononuclear cells (PBMCs) incubated with the test molecule, followed by measuring T-cell proliferation or cytokine production. If the tested molecules have immunomodulatory effects, dendritic cells (DCs) proliferation assay is recommended. In this case, the tested molecules are incubated with DCs, and co-cultured with autologous CD4+ T cells, and T-cell proliferation is measured in the final stage [71, 72].

Achieving a more comprehensive assessment of sequence-based immunogenic risk may require the use of a test panel, considering various aspects of potential responses to anti-drug antibodies. Relying on single tests might be limited in providing information regarding this risk. Therefore, an integrated approach is recommended, combining two or more tests, enabling a holistic and comprehensive understanding of immunogenic risk assignment [73].

Risk factors associated with the antibody

A crucial aspect influencing the risk of drug immunogenicity is its mechanism of action. It may contribute to the occurrence of immune complexes, nonspecific immune activation through anti-drug antibodies, and synergistic immune activation. BsAbs stimulate the immune system to generate a robust anti-tumor response, which may lead to undesired reactions. Nevertheless, immunotherapy is the standard treatment for selected types of cancers [67, 74, 75].

The formation of immune complexes between bispecific antibodies and multimeric soluble targets has not yet been confirmed with examples in oncology. However, there are associations between the formation of immune complexes and the immunogenicity of anti-inflammatory drugs. This is due to the increased capture of the therapeutic agent by antigen-presenting cells. Large immune complexes can also directly crosslink B cell receptors, leading to their activation and the production of antibodies. The stoichiometric relationships of the drug are crucial and can influence the formation of immune complexes [75–77].

Non-specific immune activation targeted at cell surface receptors, to mitigate unintended stimulation of the immune system, requires their dimerization or higher-order crosslinking. There is also the potential for using agonistic products to activate receptors, after crosslinking by anti-drug antibodies with the drug and the target, to lead to immune activation. Similarly, in the case of antagonistic products, this can activate receptors and release cytokines [78].

Immunostimulatory drugs may more frequently induce immunogenicity compared to drugs with known immunosuppressive effects. Despite this, therapy with immune checkpoint inhibitors has shown a low frequency of anti-drug antibodies. Recently, bispecific antibodies with a synergistic immunostimulatory effect, inhibiting dual checkpoints and activating immune cells, have been developed. Many of these bispecific antibodies are still in the developmental stage, however, increased immunogenicity has been observed with selected therapies combined with checkpoint inhibitors. Therefore, the occurrence of this risk should be considered before initiating therapy with specific antibodies [79, 80].

Patient-related risk factors

Previous treatments with bispecific antibodies can lead to the development of anti-drug antibodies that may cross-react with a related product, resulting in the presence of pre-existing antibodies against the new drug. Therefore, high titers may occur early on. Taking this phenomenon into account, before changing treatment, it is important to consider the patient's history, specifically the status and specificity of anti-drug antibodies, and conduct screening tests for pre-existing antibodies [81].

Factors that can influence immunogenicity and are associated with the patient's body include the route, site of administration, and dose of the drugs. In some cases, a lower sporadically administered dose may correlate with increased immunogenicity compared to a higher dose given continuously. Moreover, other studies indicate that intravenous administration is less immunogenic than subcutaneous administration. It is also worth mentioning premedication with immunosuppressants. This involves using a glucocorticoid, such as dexamethasone, before administering bispecific antibodies to dampen the immune response. However, it has not been demonstrated whether this is effective in mitigating the formation of anti-drug antibodies in bispecific antibody immunotherapy [82–84].

In conclusion, a comprehensive assessment of the patient's anti-drug antibody profile becomes a key element. This involves a thorough analysis of both the anticipated effective exposure and the recommended dosing regimens. This allows for better customization of therapy to

enhance its effectiveness and minimize potential adverse effects. Throughout this process, various factors such as the patient's genetic predispositions, the state of their immune system, and overall health status should be taken into account [69].

Adverse effects and their treatment

With advancements in the field of biological therapies, bispecific antibodies represent a promising group of drugs. However, their use comes with potential risks associated with adverse effects. The most common adverse effects include skin lesions, fatigue, nausea, vomiting, abdominal pain, as well as the occurrence of leukopenia and thrombocytopenia. A frequent effect of therapy is also the occurrence of a "cytokine storm". Symptoms related to cytokine release are also side effects of monoclonal antibodies. Some patients may experience hepatotoxicity, fever and chills, in addition to the aforementioned symptoms. Moreover, neurological side effects may occur, which are entirely reversible after the completion of therapy [46, 85–87].

To minimize cytokine release, two therapeutic strategies can be employed: corticosteroids (such as methylprednisolone) and tocilizumab, which is an interleukin-6 (IL-6) receptor antagonist [88–90]. Additionally, temporarily discontinuing BsAb treatment until the resolution of grade three or four symptoms and then gradually resuming therapy with dose escalation can be considered. According to FDA recommendations, the occurrence of a grade 4 cytokine release syndrome should result in permanent treatment discontinuation [91].

However, it should be noted that the number of reported cases resulting from the use of BsAbs is significantly lower compared to the quantity of immune-related adverse events (irAEs) associated with immune checkpoint inhibitor (ICI) therapy [92]. Adverse effects related to ICI are organ-specific, with skin-related issues being the most common, followed by gastrointestinal toxicity [93, 94]. Endocrinologic symptoms, such as pituitary inflammation, thyroid dysfunction, and adrenal insufficiency, represent the third group [95]. Adverse effects on the musculoskeletal system and eyes are also frequently reported [96]. Other serious side effects of this therapy include myocarditis, pneumonitis, nephritis, neurotoxicity, and hematologic toxicity. However, they are not very common. In most patients experiencing irAEs, the mortality rate ranges from 10% to 17%, and for myocarditis, it is as high as 39.7%. Neurotoxicity is typically more severe and can lead to brain inflammation resulting in death [97].

Treatment of immune-related adverse events begins with effective education of patients and caregivers, both before starting immune checkpoint inhibitor therapy and throughout its duration. This includes a detailed explanation of the mechanism of action of immune checkpoint inhibitors and the principles of managing immune-related adverse events. Additionally, continuous monitoring of the level of immune-related adverse events is essential. If they occur, consideration should be given to discontinuing or completely stopping ICI therapy, depending on the degree of toxicity. For most grade II irAEs, initiation of corticosteroid therapy is considered. In grade III, corticosteroid therapy is also necessary but in high doses, gradually tapering over 4-6 weeks. However, if symptoms do not resolve within a few days, immunosuppressive drugs may also be considered [96, 98].

To avoid potential adverse effects, a crucial element is an individualized approach to each patient. Regular monitoring, both clinically and through laboratory tests, allows for early detection of any abnormalities. Patient education regarding reporting any symptoms and consulting with the medical team is an integral part of the strategy to avoid adverse effects of bispecific antibody therapy. It is worth emphasizing that continuous scientific research and the development of monitoring methods are essential to refine this innovative form of therapy, aiming to minimize, as much as possible, potential risks for patients [99, 100].

Summary

The development of new technologies for obtaining bispecific antibodies has enabled the construction of various formats, increasing therapeutic efficacy and safety in the treatment of cancer. These antibodies play a significant role in regulating signaling pathways, counteracting angiogenesis, and controlling the tumor microenvironment. Despite promising advances in the application of BsAbs in certain types of cancer, achieving greater effectiveness in the treatment of solid tumors still requires intensive research, as their development is much more complex compared to monoclonal antibodies. With the introduction of increasingly diverse BsAbs into preclinical and clinical studies, various challenges arise, complicating the development of these substances.

A crucial step in designing bispecific antibodies is the selection of an optimal combination of targets, followed by choosing the appropriate format and developing the molecule in line with therapeutic goals and disease biology. Additionally, improper clinical design and dosing regimens can expose patients to increased toxicity, which can be somewhat minimized through the optimization of treatment strategies, dosing, and administration sequences. It is believed that

many issues arising during research and development processes will be gradually resolved over time.

Dynamic progress in the field of bispecific antibodies is considered a key revolutionary factor in cancer treatment. Continuous innovations in design, technology, and the understanding of cancer biology mechanisms will significantly contribute to more effective and personalized therapeutic strategies. Therefore, bispecific antibodies have substantial potential to transform the approach to cancer treatment.

Article Information and Declarations

Author contributions

A.B.: article concept, writing, literature data collection; K.W.-K.: article concept, writing, supervising the article; N.K.: article concept, writing, literature data collection; P.K.: article concept, writing, supervising the article. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

None.

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