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Nonclinical Safety Assessment of Bispecific Antibody-Drug Conjugates (BsAb-ADC) in Repeat-Dose Toxicity Studies

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Highlight

This study aimed to characterize the nonclinical safety profile of Bispecific Antibody-Drug Conjugates (BsAb-ADCs) in repeat-dose toxicity studies. A key finding was the off-target toxicities impacting liver, kidney, heart, and lungs, along with bone marrow suppression, immune system stimulation and neurotoxicity. Additionally, skin and ocular toxicities were also noted, particularly in microtubule inhibitor-based BsAb-ADCs. The research underscores the importance of adopting a comprehensive approach to safety assessment, which integrates pathological analysis, toxicokinetics, and immune response monitoring, to predict and evaluate potential toxicities early in development. These insights are crucial for optimizing safety strategies and guiding clinical development of BsAb-ADCs.

Background

BsAb-ADCs represent an innovative class of therapeutics that integrate bispecific antibodies with cytotoxic payloads. This dual-targeting mechanism enhances the efficacy of tumor cell elimination while improving specificity for cancer cells. However, the complex structure may pose potential risks, such as off-target toxicity and immune responses, particularly when administered repeatedly. The goal of this study is to systematically analyze specific toxic reactions and their underlying mechanisms, and to optimize safety assessment strategies and provide scientific guidance for the development of these therapeutics.

Methods

The study summarizes multiple GLP toxicity data of various BsAb-ADCs conducted in TriApex, utilizing both rodent and non-rodent animal models. The primary objective is to investigate the toxicological responses associated with various BsAb-ADCs during repeat-dose administration. Particular emphasis is placed on understanding how dual-targeting affects non-target tissues, such as the liver, kidneys, heart, and lungs, as well as bone marrow suppression, immune system activation, nervous system effects, skin toxicity, and ocular toxicity. By integrating pathological findings with toxicokinetic data, the study provides an in-depth examination of the mechanisms underlying different toxic reactions and identifies key risk factors.

Results

In the repeat-dose toxicity studies of BsAb-ADCs, several major toxic reactions were observed:

(1) Off-Target Toxicity: The dual-targeting nature of BsAb-ADCs can lead to unintended binding to non-target tissues, especially when one/both target(s) is/are expressed in normal tissues. Common off-target toxicities include damage to liver, kidneys, heart, and lungs. Pathological findings include hepatocellular degeneration, renal tubular epithelial cell damage, myocardial inflammation, interstitial lung injury, alveolar damage, and pulmonary inflammation.

(2) Bone Marrow Suppression: BsAb-ADCs may induce bone marrow suppression manifested by decreased levels of red blood cells, white blood cells, and platelets, thereby impairing hematopoietic function. High doses and prolonged treatment can exacerbate this effect, potentially leading to compromised immune function.

(3) Immune System Stimulation: In non-human primate studies, BsAb-ADCs were found to activate the immune system, resulting in side effects such as complement activation, inflammatory responses, and thrombocytopenia. The dual-target structure may cause non-specific activation or inhibition of the immune system, increasing the risk of immune dysfunction.

(4) Neurotoxicity: Some BsAb-ADCs may induce neurotoxicity through immune system stimulation or direct effects on the nervous system. These toxicities are often associated with cytokine release syndrome (CRS) and immune-mediated inflammatory responses, presenting as seizures, confusion, drowsiness, headaches, and tremors. Additionally, the cytotoxic components (such as microtubule inhibitors) may directly damage nerve cells, resulting in nervous system disorders such as tremors, limb numbness, and ataxia.

(5) Skin and Ocular Toxicity: Skin toxicity is manifest by localized inflammatory reactions at the injection site, as well as systemic rashes and itching. Furthermore, BsAb-ADCs containing microtubule inhibitors may cause ocular toxicity, characterized by symptoms like corneal opacity, retinal damage, and even vision impairment or corneal injury.

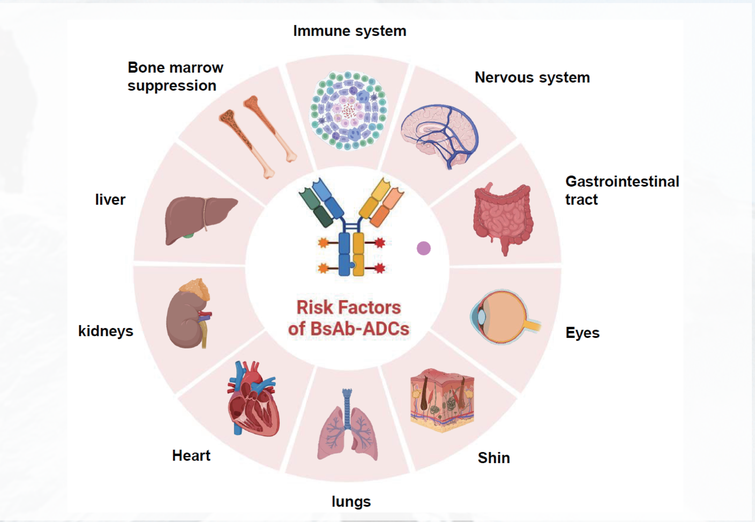

Figure 1. Risk Factors and Affected Organs in BsAb-ADCs Repeat-dose Toxicity Studies

Conclusion

The nonclinical safety evaluation of BsAb-ADCs requires a focus on the complex toxicity profile resulting from their dual-target design. It is recommended to integrate pathological analysis, toxicokinetic studies, and immune response monitoring in toxicity testing to systematically assess tissue- and organ-specific toxicities, particularly mechanisms related to complement activation, off-target effects, and specific organ toxicity. By employing scientifically sound toxicity study designs and comprehensive in vivo and in vitro assessments, it is possible to predict and evaluate the potential toxicity of BsAb-ADCs at an early stage, thereby providing reliable support for decision-making and subsequent clinical development.

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