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Decoding Haematological Toxicity Associated with Antibody-Drug Conjugates: Mechanisms, Clinical Profiles and Management Strategies

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ABSTRACT

Antibody-drug conjugates (ADCs) improve targeted drug delivery but are often associated with hematological toxicity. This review examines the structural, mechanistic and clinical evidence on ADC-induced hematological toxicity, focusing on approved ADCs and strategies for dose adjustment. Approved ADCs, including Gemtuzumab Ozogamicin (GO), Inotuzumab Ozogamicin (IO), trastuzumab emtansine, brentuximab vedotin, Polatuzumab Vedotin (PV), Sacituzumab Govitecan (SG), trastuzumab deruxtecan, Enfortumab Vedotin (EV), tisotumab vedotin, Loncastuximab Tesirine (LT), belantamab mafodotin, mirvetuximab soravtansine and disitamab vedotin, exhibit distinct hematological toxicity profiles. Common adverse events include neutropenia, thrombocytopenia, anemia, leukopenia, lymphopenia and febrile neutropenia. These toxicities are influenced by factors such as antigen distribution, linker stability, payload characteristics, drug-to-antibody ratio, Fc receptor-mediated uptake and nonspecific endocytosis. Management strategies include dose interruption or reduction, growth factor support, transfusions and regular laboratory monitoring. Hematological toxicity is an important factor affecting the tolerability of ADCs. Understanding the mechanisms underlying these toxicities is essential for improving their clinical management and guiding the development of safer next-generation ADCs.

INTRODUCTION

Overview of antibody-drug conjugates (adcs) as targeted cancer therapy: Antibody-Drug Conjugates (ADCs) are an important class of targeted anticancer therapies that combine the targeting specificity of monoclonal antibodies with the high potency of cytotoxic agents. Compared with conventional chemotherapy, ADCs are designed to improve the selective delivery of cytotoxic drugs to tumour cells while limiting exposure to healthy tissues. The general architecture of ADCs comprises three linked components: A monoclonal antibody that targets a tumour-associated antigen, a chemical linker and a cytotoxic drug payload. The therapeutic efficacy of ADCs depends on selective antigen binding, receptor-mediated endocytosis, intracellular payload release and subsequent tumour cell death. Over the past two decades, ADCs have evolved from an extension of the "magic bullet" concept into an established therapeutic modality. As of 2023, 14 ADCs had received regulatory approval, with the number expected to reach 15 by 2024. This progress has been driven by advances in linker design, the development of novel cytotoxic payloads and the identification of new therapeutic targets. ADCs are increasingly used to treat both haematological malignancies and solid tumours, including leukaemia, lymphoma, breast cancer, urothelial cancer and ovarian cancer. Ultimately, ADCs aim to improve therapeutic efficacy by enhancing tumour cell elimination while minimising exposure to healthy tissues[1-4]

Importance, purpose and scope of the review: Investigating hematological toxicity associated with ADCs is important because myelosuppression is one of the most common and clinically significant toxicities associated with this class of drugs.

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Although, ADCs are designed to reduce nonspecific toxicity through targeted drug delivery, hematological adverse events, including anaemia, neutropenia, febrile neutropenia and thrombocytopenia, remain important clinical concerns. These toxicities may arise through several mechanisms, including premature payload release, Fc receptor-mediated interactions with healthy cells and nonspecific cellular uptake. As reported by Ballestín *et al.*[2], among patients with haematological malignancies, the incidence of grade 3 or higher neutropenia exceeded 20% for most approved ADCs, whereas gemtuzumab ozogamicin was associated with grade 3 or higher thrombocytopenia in 100% of patients and anaemia in 86.2%. Hematological toxicity also remains a significant concern in patients with solid tumours. For example, sacituzumab govitecan was associated with grade 3 or higher neutropenia in 51% of patients, while trastuzumab deruxtecan was associated with grade 3 or higher neutropenia in 19.05% of patients. Such toxicities may lead to infections, bleeding, dose interruptions, treatment discontinuation and potentially reduced treatment effectiveness, highlighting the importance of systematically characterising and managing ADC-associated hematological toxicity.

This review aims to summarise current knowledge of ADCs, with particular emphasis on their associated hematological toxicity, from structural, mechanistic and clinical perspectives. Specifically, it describes the structure and mechanisms of action of ADCs, identifies the major hematological toxicities reported for currently approved ADCs, examines the contributions of the antibody, linker, payload and target-antigen expression to these toxicities and discusses strategies for improving ADC safety while preserving therapeutic efficacy[1-4]

ADC structure and mechanism of action:

Composition: monoclonal antibody, linker and cytotoxic drug: ADCs are sophisticated bioconjugates comprising three principal components: a tumour-targeting monoclonal antibody (mAb), a chemical linker and a highly potent cytotoxic drug molecule. The monoclonal antibody serves as the targeting component by recognising tumour-associated antigens (TAAs) expressed on the surface of cancer cells. Most FDA-approved ADCs (13 out of 15) are based on the Immunoglobulin G1 (IgG1) subclass, accounting for 86.7% of the approved agents considered. This predominance reflects the Favourable Pharmacokinetic (PK) properties of IgG1 antibodies, including a serum half-life of approximately 21 days, as well as their capacity to mediate antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis and complement-dependent cytotoxicity. Early ADCs were developed using murine antibodies, which could elicit strong immune responses. More recent ADCs predominantly use humanised or fully human monoclonal antibodies to reduce immunogenicity[1,3,5]

The linker connects the antibody to the cytotoxic payload and helps determine ADC stability during blood circulation and payload release within target cells. Linkers are broadly classified as cleavable or non-cleavable. Cleavable linkers include cathepsin-sensitive peptide linkers, pH-sensitive hydrazone linkers and disulfide linkers. These linkers are designed to facilitate payload release in response to specific intracellular or microenvironmental conditions. According to the reported classification, cleavable linkers are used in 73.3% of approved ADCs. Their design must balance stability in systemic circulation with efficient payload release at the intended site of action[1,5,6].

The cytotoxic payload is the pharmacologically active component of an ADC and can be classified into three major groups: Tubulin inhibitors, DNA-damaging agents and topoisomerase I (TOP1) inhibitors. Tubulin inhibitors include auristatins, such as monomethyl auristatin E (MMAE) and monomethyl auristatin F (MMAF) and maytansinoids, such as DM1 and DM4. DNA-damaging agents include calicheamicins and pyrrolobenzodiazepine (PBD) dimers. TOP1 inhibitors include deruxtecan (DXd) and SN-38, the active metabolite of irinotecan. The drug-to-antibody ratio (DAR) represents the average number of payload molecules conjugated to each antibody and plays an important role in determining ADC pharmacokinetics, stability and toxicity. Variability in DAR arising from non-site-specific conjugation can contribute to heterogeneous ADC populations and may adversely affect pharmacokinetic properties and systemic tolerability[1,5,6]

Mechanism of action: ADCs are initially distributed through the bloodstream, where the antibody component specifically binds to tumour-associated antigens (TAAs) overexpressed on cancer cells. Ideal target antigens should be highly expressed on the surface of cancer cells, have minimal expression in normal tissues, remain cell-associated rather than being secreted and undergo rapid receptor-mediated endocytosis. Following antigen binding, the ADC-antigen complex is internalised through clathrin-mediated endocytosis (CME), Caveolin-dependent Endocytosis (CDE), or alternative clathrin- and caveolin-independent endocytic pathways. The internalised complex then progresses through the endosomal pathway from early to late endosomes. Notably, only approximately 1% of the administered ADC dose reaches the tumour.

Following internalisation, the ADC-antigen complex is trafficked to lysosomes, where enzymatic degradation or chemical cleavage facilitates the release of the cytotoxic payload, depending on the ADC's design. Tubulin-targeting payloads, such as MMAE and DM1, disrupt microtubule dynamics, leading to G2/M cell-cycle arrest and apoptotic cell death. In contrast, DNA-damaging payloads, such as calicheamicin and pyrrolobenzodiazepine (PBD) dimers, induce DNA damage, including double-strand breaks,

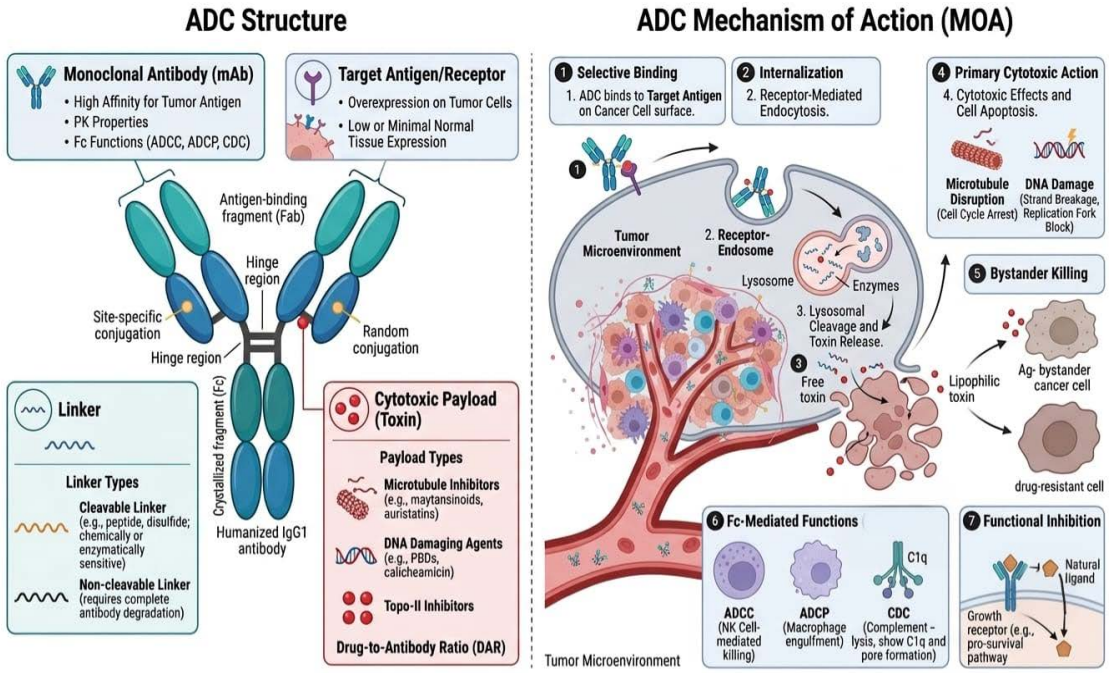


Fig. 1: ADC structure and mechanism of action

resulting in cell death. Topoisomerase I (TOP1) inhibitors, such as DXd and SN-38, inhibit DNA replication by stabilising the TOP1-DNA cleavage complex. Some membrane-permeable payloads released from ADCs containing cleavable linkers can diffuse into neighbouring tumour cells that lack the target antigen, producing a bystander effect. The persistence of ADCs in the circulation can provide sustained payload delivery; however, the extent and duration of payload exposure depend on the ADC's pharmacokinetic properties, linker stability and payload-release characteristics[1,5,6].

Antibody-drug conjugates (ADCs) comprise a monoclonal antibody, a linker and a cytotoxic payload. Following antigen binding, ADCs are internalised and trafficked to lysosomes, where payload release induces tumour cell death through mechanisms such as microtubule inhibition or DNA damage. Some ADCs also mediate a bystander effect and may engage Fc-dependent immune functions[1,3,4] (Fig. 1).

Haematological toxicities seen with ADCS: Myelosuppression or haematological toxicity is among the most commonly observed dose-limiting adverse effects of ADC therapy. These toxicities comprise a significant proportion of all adverse events, with incidences of up to 42% reported in Phase II/III trials. Such toxicities are attributed to the non-specific delivery of cytotoxic molecules to the bone marrow, instability of the chemical linker and antigen expression in blood cell precursor cells. Pharmacovigilance data indicate that haematological adverse events are associated with high rates of hospitalisation (30.38%) and mortality (18.30%), highlighting the need for vigilant monitoring[7].

Neutropenia and febrile neutropenia[7-9]: Neutropenia is the most commonly reported haematological adverse effect associated with several ADCs.

Clinical relevance: Neutropenia is the most frequently reported blood-related adverse event. In clinical trials of Sacituzumab Govitecan (SG), all-grade neutropenia occurred in up to 63% of subjects, while Grade 3+ neutropenia was reported in 51%. Febrile neutropenia, a serious complication, was reported in 6% of patients receiving SG, while a significant risk has also been observed with Brentuximab Vedotin (BV).

Associated ADCs: High-risk signals have been observed in association with Sacituzumab Govitecan (SG), Polatuzumab Vedotin (PV), Loncastuximab Tesirine (LT) and Brentuximab Vedotin (BV). High rates of neutropenia have also been reported with trastuzumab deruxtecan (T-DXd), occurring in approximately 29% of cases.

Mechanism:

Linker instability: ADCs with Val-Cit (valine-citrulline) cleavable linkers, such as BV, PV and EV, can be hydrolysed by neutrophil elastase. This enzyme is secreted by maturing neutrophils in the bone marrow. Hydrolysis can cause the release of toxic free payloads, such as MMAE, directly within the bone marrow, thereby leading to the destruction of maturing neutrophils.

Type of payload: ADCs containing microtubule inhibitors (auristatins) and topoisomerase I inhibitors (SN-38 and DXd) have stronger associations with neutropenia than ADCs containing other payload types.

Thrombocytopenia[7,8,10]: Thrombocytopenia, or low platelet counts, is a major adverse effect that can result in treatment delays or discontinuation.

Clinical relevance: The incidence of thrombocytopenia is particularly associated with ado-trastuzumab emtansine (T-DM1), with Grade 3 thrombocytopenia occurring at a rate of 34.6% in some head-to-head studies, which is substantially higher than that reported with T-DXd. Gemtuzumab ozogamicin (GO) and inotuzumab ozogamicin (IO) have the strongest associations with thrombocytopenia, with thrombocytopenia occurring in 77% of patients in some IO clinical trials.

Associated ADCs: T-DM1, gemtuzumab ozogamicin (GO), Inotuzumab Ozogamicin (IO) and loncastuximab tesirine (LT).

Mechanism

Fc-receptor-mediated entry: One major pathophysiological mechanism underlying T-DM1-mediated thrombocytopenia involves the uptake of the ADC by megakaryocytes, the precursors of platelets, via FcγRIIa. Inside these cells, the DM1 payload interferes with microtubule formation, thereby preventing the differentiation of megakaryocytes into platelets.

Expression of off-target antigen: In GO, the cluster of differentiation 33 (CD33) antigen is expressed on myeloid progenitors and can cause direct toxicity to platelet precursors.

Anaemia[7,8,11]

Clinical relevance: Anaemia is observed with almost all ADCs currently on the market. It occurs in approximately 34% of patients receiving SG, 31% receiving T-DXd and 68% receiving polatuzumab vedotin (all grades). Grade 3/4 anaemia has been associated most frequently with MMAE-containing ADCs, occurring in approximately 6.8% of cases in a pooled analysis.

Associated ADCs: PV, tisotumab vedotin, LT, enfortumab vedotin, T-DXd and T-DM1 have the strongest associations with anaemia.

Mechanism: The direct toxicity of topoisomerase I payloads (SN-38 and DXd), as well as microtubule inhibitors, can affect erythroid progenitors in the bone marrow. This is evidenced by reductions in reticulocyte counts, haemoglobin and haematocrit, accompanied by depletion of erythroblasts and myelocytes in the bone marrow. Because red blood cell precursors proliferate rapidly, they are also susceptible to off-target cytotoxic effects, contributing to anaemia and, in some cases, broader myelosuppression.

Other haematological toxicities[7,12]

Leukopenia: Reduction in the white blood cell count, usually following a pattern similar to that of neutropenia. For SG, the incidence of this toxicity was 16% in the ASCENT study.

Lymphopenia: Occurs most frequently when the ADC targets lymphocytes. Polatuzumab vedotin, which targets cluster of differentiation 79b (CD79b), has been associated with lymphopenia rates of up to 80% in some studies. Lymphopenia is also a common adverse reaction associated with brentuximab vedotin and mirvetuximab soravtansine.

Pancytopenia: Reduction in red blood cells, white blood cells and platelets, indicative of bone marrow suppression.

Bone marrow failure/aplasia: Failure of the bone marrow to produce blood cells. Febrile bone marrow aplasia is a specific risk marker associated with gemtuzumab ozogamicin, brentuximab vedotin and sacituzumab govitecan.

Haemorrhage: A clinical consequence of severe thrombocytopenia caused by ADC therapy. Haemorrhage is included in the label warnings for several ADCs.

Approved ADCs are summarised according to their target antigen, payload, linker type, indication and reported haematological adverse events. Table 1 highlights the most common cytopenias, including neutropenia, thrombocytopenia and anaemia, together with clinically relevant associated toxicities such as febrile neutropenia and veno-occlusive disease[7,11,12].

Pathophysiological mechanisms of ADC-induced haematological toxicity

Off-target toxicity mechanisms: Despite the design of ADCs to specifically deliver highly potent payloads to antigen-expressing tumour cells, the haematological toxicity of these drugs is generally associated with off-target effects rather than tumour-restricted activity alone. The primary mechanism of ADC-related toxicity is the premature systemic release of payloads due to insufficiently stable linkers, which allows circulating free cytotoxins to affect rapidly dividing normal tissues, including the bone marrow. Clinically, the relevance of this pathway stems from the relatively small proportion of the payload that is actually delivered to tumour cells compared with the proportion that remains systemically available or is degraded in healthy tissues. In addition, intact ADCs may enter non-target cells

Table 1. Hematologic toxicity profile of approved ADCs

ADC (approval, year)	Target antigen/payload/linker	Indication	Neutropenia/leukopenia	Th20rombocytopenia	Anaemia/↓haemoglobin	Other hematologic/related aes
Gemtuzumab ozogamicin[31]	CD33/N-acetyl-γ-calicheamicin/ cleavable (hydrazone), DAR-2-3	CD33+AML	Reported (dose-limiting)	Grade ≥3 (PLT<50 G/L): 19%	Reported	Hepatic veno-occlusive disease (VOD/SOS); 3 patient deaths due to VOD in early trials; infusion reactions
Brentuximab vedotin[32]	CD30/MMAE/cleavable (Val-Cit), DAR 4	Relapsed/refractory Hodgkin lymphoma; systemic ALCL	cHL: 54%; sALCL: 55% (all grades)	cHL: 28%; sALCL: 16% (all grades)	cHL: 33%; sALCL: 52% (all grades)	Peripheral neuropathy, febrile neutropenia; myelotoxicity was dose-limiting toxicity in nonclinical studies
Trastuzumab emtansine (T-DM1)[33]	HER2/DM1 (maytansinoid)/ non-cleavable (SMCC), DAR 3.5	HER2+metastatic breast cancer	6.7% (all grades)	31.2% (all grades); dose-limiting in nonclinical models via FcγRIIa-mediated megakaryocyte uptake	14.3% (all grades)	Hepatotoxicity (↑AST/ALT); cardiotoxicity; peripheral neuropathy
Inotuzumab ozogamicin[34]	CD22/N-acetyl-γ-calicheamicin /cleavable (hydrazone), DAR 6	Relapsed/refractory B-cell precursor ALL	49% (all grades)	51% (all grades); dose-limiting	36% (all grades)	Febrile neutropenia 26%; leukopenia 35%; lymphopenia 18%; VOD/SOS 14%
Polatuzumab vedotin[35]	CD79b/MMAE/cleavable (Val-Cit), DAR 3.5	Relapsed/refractory diffuse large B-cell lymphoma	60% (all grades)	32% (all grades)	68% (all grades)	Lymphopenia 80%; febrile neutropenia 15%; peripheral neuropathy; hepatotoxicity
Fam-trastuzumab deruxtecan (T-DXd)[36]	HER2/DXd (TOP1 inhibitor)/ cleavable (tetrapeptide), DAR 8	HER2+advanced/ metastatic breast cancer	29% (all grades); leukopenia 22%	20% (all grades)	31% (all grades)	Highest systemic free-payload concentration among approved ADCs; interstitial lung disease (dose-limiting, non-hematologic)
Enfortumab vedotin[37]	Nectin-4/MMAE/cleavable (Val-Cit), DAR 3.8	Advanced/metastatic urothelial cancer	14% (grades 2-4)	Not prominently reported	34% (grades 2-4)	Lymphopenia 32%; peripheral neuropathy; hyperglycemia; skin toxicity
Sacituzumab govitecan[38]	TROP-2/SN-38 (TOP1 inhibitor) /cleavable (CL2A), DAR 7.6	Metastatic triple-negative breast cancer; urothelial cancer	64% (all grades); grade ≥3: 49%	Reported (nonclinical bone-marrow suppression)	Reported	Febrile neutropenia 6%; neutropenic colitis 1.4%
Belantamab mafodotin[39]	BCMA/MMAF/non-cleavable (maleimidocaproyl), DAR~2.5-4	Relapsed/refractory multiple myeloma	28% (all grades)	62% (all grades); dose-limiting	Reported (HGB decreased 32%)	Ocular toxicity/keratopathy (dose-limiting, non-hematologic); lymphopenia 49%
Tisotumab vedotin[40]	Tissue factor/MMAE/cleavable (Val-Cit), DAR 4	Recurrent/metastatic cervical cancer	21% (all grades); leukopenia 30%	Not prominently reported	52% (↓HGB, all grades)	Lymphopenia 42%; haemorrhage 62% (all grades), grade ≥3: 5%; ocular toxicity
Disitamab vedotin[41]	HER2/MMAE/cleavable (Val-Cit), DAR 4	Advanced/metastatic gastric, breast, urothelial cancer	Grade ≥3 (serious AE)	Not prominently reported	Not prominently reported	GI reactions; peripheral neuropathy; ↑bilirubin
Loncastuximab tesirine[42]	CD19/SG3199 (PBD dimer)/ cleavable (Val-Ala), DAR 2.3	Relapsed/refractory large B-cell lymphoma/high-grade B-cell lymphoma	52% (all grades)	58% (all grades); dose-limiting (lowest DAR of approved ADCs)	51% (↓HGB, all grades)	Skin pigmentation/rash; hepatotoxicity; pericardial effusion
Mirvetuximab soravtansine[43]	Folate receptor-α/DM4 (maytansinoid)/cleavable (sulfo-SPDB), DAR 3.4	Folate receptor alpha+ platinum-resistant ovarian, fallopian tube, peritoneal cancer	26% (all grades); leukopenia 26%	18% (all grades)	25% (↓HGB, all grades)	Lymphopenia 35%; ocular toxicity; peripheral neuropathy; ↑ALT/AST/ALP

CD19: Cluster of differentiation 19, BCMA: B-cell maturation antigen and HER2: Human epidermal growth factor receptor 2

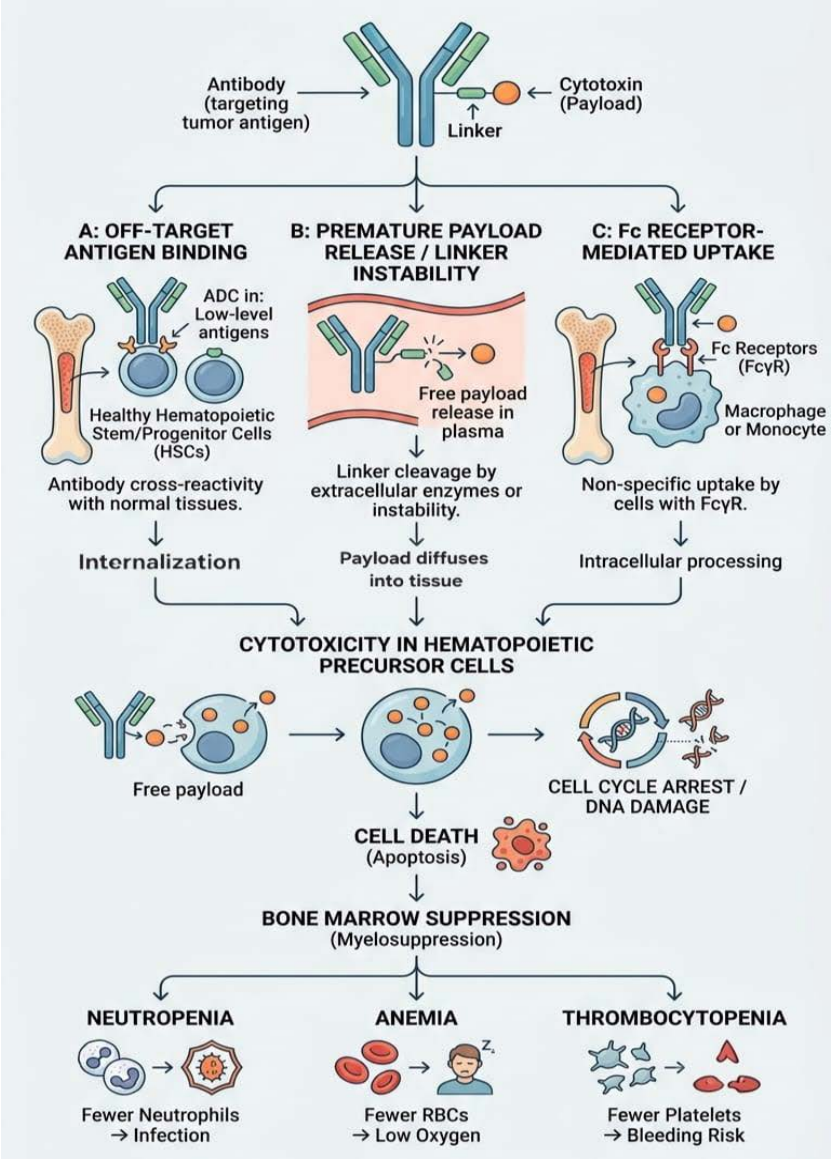


Fig. 2: Mechanisms of ADC-associated hematologic toxicity

through Fc-receptor-mediated internalisation and non-selective endocytic pathways, such as macropinocytosis. In this context, it is important to note that bone marrow cells can internalise ADCs even in the absence of the intended target antigen. Furthermore, the bystander effect may contribute to haematological toxicity because membrane-permeable payloads can diffuse out of target cells and affect neighbouring antigen-negative stromal or progenitor cells[1,5,9,13].

ADCs can cause myelosuppression through off-target antigen binding, premature payload release due to linker instability and Fc receptor-mediated uptake by haematopoietic cells. These mechanisms can induce cytotoxicity in haematopoietic precursor cells, resulting in cell-cycle arrest, DNA damage, apoptosis and bone marrow suppression. Clinically, these effects may manifest as neutropenia, anaemia and thrombocytopenia[1,5,9] (Fig. 2).

Impact of linker stability and payload properties: Linker chemistry plays an important role in haematological toxicity because of its influence on the location, timing and efficiency of payload release. Cleavable linkers are engineered to become activated under acidic conditions, in the presence of glutathione, or through the action of lysosomal enzymes. However, if such a linker is hydrolysed in plasma before reaching the tumour site, the released payload can damage bone marrow cells. The hydrazone-linked calicheamicin conjugate gemtuzumab ozogamicin serves as an example of this phenomenon, as linker instability resulted in premature drug release and caused significant systemic toxicities, including haematological adverse effects. Non-cleavable linkers generally exhibit greater stability in plasma but they are not always safer because of the accumulation of intracellular catabolites.

Payload properties are equally important. Drugs that inhibit tubulin, such as DM1, DM4, MMAE and MMAF, disrupt microtubule dynamics in dividing cells and have been associated with the development of cytopenias, particularly thrombocytopenia with maytansinoid drugs and general bone marrow suppression with auristatins. Membrane permeability is also important, as diffusible payloads can cause bystander damage, whereas hydrophobic combinations of the payload and linker can lead to aggregation, altered biodistribution and non-specific uptake. In addition, a higher Drug-to-antibody Ratio (DAR) can increase systemic exposure and has been correlated with haematological toxicity, as demonstrated in a pooled clinical study[1,5,9,13].

Effects on bone marrow progenitor cells: Bone marrow progenitor cells are primarily responsible for the cytopenias associated with antibody-drug conjugates (ADCs). Their rapid proliferation renders haematopoietic progenitor cells and precursors particularly susceptible to disruptions in DNA replication, mitotic spindle function and cytoskeletal dynamics. Thrombocytopenia provides a good illustration of this mechanism. The T-DM1 can be internalised by megakaryocytes through FcRIIa-mediated uptake, whereby DM1 inhibits microtubule formation and thereby blocks proplatelet production and maturation. Blockade of the FcRIIa receptor does not completely prevent uptake, suggesting that alternative routes, such as macropinocytosis, can facilitate ADC entry into bone marrow precursors. As such, thrombocytopenia may arise independently of the presence of the target antigen on megakaryocytes. Similar pathways may underlie neutropenia and anaemia, given the detrimental effects of payloads on myeloid and erythroid progenitors. Consequently, haematological toxicity can result from reduced bone marrow output and the accumulation of cytopenias over successive treatment cycles. In patients with haematological malignancies or those who have undergone intensive treatments, haematological toxicity is a frequent adverse effect because of the increased sensitivity of the bone marrow[1,5,9,13].

Immune-mediated mechanisms: In addition to direct progenitor toxicity, immune-related mechanisms can add another layer of complexity, particularly when immune mechanisms are not the principal mode of action of the drug. Interaction of the Fc region with Fc receptors on effector or stromal cells can lead to unintended internalisation, cytokine production and local inflammation, resulting in damage to haematopoiesis. Furthermore, the use of hydrophobic linkers and payloads in heterogeneous conjugation can increase the tendency for aggregation and immunogenicity, leading to the development of antibodies against the drug or the formation of immune complexes. This, in turn, can alter ADC pharmacokinetics and increase their non-specific distribution throughout the body. Finally, ADCs can cause immune-mediated adverse events through antibody- or payload-mediated activation of inflammatory pathways[1,9].

Factors influencing haematological toxicity:

ADC Design:

The design of an ADC is an important determinant of haematological toxicity. Key determinants include antibody specificity, linker technology, payload type, conjugation method and DAR. The antibody should specifically bind antigens that are highly expressed by malignant cells and minimally expressed by normal tissues to minimise on-target, off-tumour binding and Fc-mediated internalisation in normal cells. Antigen selection is also important in terms of internalisation; Rapid endocytosis favours tumour delivery, whereas low-specificity or heterogeneous antigen expression can increase systemic exposure and myelotoxicity. Linker technology is also important. Cleavable linkers facilitate intracellular drug release but premature payload release in plasma can increase myelosuppression. Although, non-cleavable linkers are generally stable in plasma, clinical trials have shown that they can also increase haematological adverse effects because of intracellular metabolism. Payload type and mechanism of action also influence haematological side effects; tubulin inhibitors (e.g., auristatins and maytansinoids) can cause cytopenias in rapidly dividing bone marrow cells and different payloads can produce distinct patterns of adverse effects (e.g., DM1-induced thrombocytopenia). A high or heterogeneous DAR can influence ADC stability, distribution and pharmacokinetics; a DAR >4 has been associated with an 18.3-fold increase in the risk of haematological toxicity[14,15].

Patient-related factors: Patient-level factors significantly influence the risk of haematological toxicity. Age is relevant because older patients typically have decreased bone marrow reserves, a greater number of comorbid conditions and organ dysfunction, which can lead to higher ADC exposure or delayed recovery from cytopenias. Genomic background and other omics information may influence the risk of toxicity because of differences in antigen expression, immune responses, payload processing and susceptibility to bone marrow damage. Prior treatment is crucial, as many patients have previously received extensive therapy, including chemotherapy, radiotherapy, stem cell transplantation, or previous targeted treatments, which can cause long-lasting bone marrow damage and decreased tolerance to subsequent cytotoxic therapy. For instance, 94% of patients in the Phase I study by Tan *et al.*[9] had prior exposure to chemotherapy, with a median of three lines of treatment. Haematological malignancy itself can impair baseline bone marrow function and increase the risk of neutropenia, anaemia, or thrombocytopenia, even in the absence of direct bone marrow damage caused by ADCs[16-18].

Regimens and pharmacokinetics of dosing: Dosing regimens and pharmacokinetic properties are key determinants of haematological toxicity because most ADC-related adverse effects are exposure-dependent. Higher doses, prolonged treatment periods and multiple treatment cycles can lead to increasing cumulative stress on the bone marrow, while early-phase studies may reveal greater toxicity as patients are exposed to a wider range of doses until an optimised regimen is established. Pharmacokinetics depend on linker stability, payload hydrophobicity and DAR. These parameters influence the duration of systemic circulation and off-target exposure of the bone marrow through tissue distribution. Thus, dose limitations informed by pharmacokinetic modelling, fractionated dosing and dose reduction based on treatment response are essential strategies for decreasing peak exposure and preventing myelotoxicity while retaining therapeutic efficacy. Experience with gemtuzumab ozogamicin provides useful insights in this context[14-16,18,19].

Clinical manifestations and diagnosis

Signs and symptoms: The signs and symptoms of ADC-related haematological toxicity include those associated with neutropenia, anaemia and thrombocytopenia, which are the three most common cytopenias. Neutropenia usually does not manifest clinically until an infection occurs, which may present with fever, chills and oral ulcers, while febrile neutropenia has been reported as a dose-limiting toxicity for agents such as trastuzumab deruxtecan and sacituzumab govitecan. Anaemia is typically characterised by fatigue, pallor, dyspnoea on exertion and decreased exercise tolerance and has been reported in more than 30% of patients receiving trastuzumab deruxtecan. Thrombocytopenia is characterised by easy bruising, petechiae, epistaxis and gingival bleeding and can be particularly severe with agents such as gemtuzumab ozogamicin, for which Grade 3 or higher thrombocytopenia has been reported in 100% of patients undergoing treatment[1,2,9,13].

Laboratory testing and biomarkers: Serial Complete Blood Counts (CBCs) with differential are used to monitor cytopenias, including neutrophil, haemoglobin and platelet counts and to guide dosing modifications, including dose withholding or reduction according to toxicity grade in HER2-targeting ADC protocols. Liver function testing, including alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin, is performed because hepatotoxicity may coexist with haematological toxicity, particularly with calicheamicin-containing ADCs such as gemtuzumab and inotuzumab ozogamicin. Bone marrow biopsy is generally performed only in cases of persistent or unexplained cytopenia after 3 months to exclude bone marrow infiltration, myelodysplasia, or bone marrow failure. Emerging biomarkers include baseline plasma IgG levels, as low levels may predispose patients to increased ADC clearance through Fc-receptor-mediated pathways, potentially contributing to thrombocytopenia and neutropenia. Inflammatory markers, such as C-reactive protein and ferritin, may be useful when inflammation is considered to contribute to cytopenia. Transcriptional and pharmacokinetic analyses of target antigen expression and drug-to-antibody ratio heterogeneity are being investigated to identify patients at high risk of myelosuppression[2,9,13,20,21].

Differential diagnosis: Because haematological abnormalities in oncology patients are multifactorial, it is important to exclude alternative diagnoses before attributing cytopenia to ADC therapy. Bone marrow progression or infiltration by cancer cells, particularly in haematological malignancies, can independently cause cytopenias that may be indistinguishable from treatment-related toxicity; therefore, assessment of baseline bone marrow reserve should be considered. Previous exposure to, or concomitant use of, chemotherapy, radiotherapy, or stem cell transplantation should also be considered, as patients with extensive prior treatment may have reduced bone marrow reserve, which can complicate attribution of cytopenias to ADC therapy. Various infections, including cytomegalovirus (CMV) and/or Herpes Simplex Virus (HSV) reactivation and bacterial infections, may occur in immunocompromised patients and should be excluded using blood cultures and viral Polymerase Chain Reaction (PCR) testing when clinically indicated. Immune-mediated mechanisms of cytopenia, such as Fc-receptor-mediated immune complex clearance in ADC-induced thrombocytopenia, should be considered separately from direct bone marrow toxicity. Medications, nutritional deficiencies and hepatic or renal dysfunction that may contribute to or exacerbate ADC-induced myelosuppression should also be evaluated[9,13,20,21].

Management and supportive therapy

Guidelines for dose modification and treatment interruption: Management of haematological toxicity associated with ADCs involves early intervention, treatment interruption until recovery and dose reductions rather than permanent discontinuation, as most reactions are reversible with appropriate supportive care. Across available ADCs, Grade 3+ events frequently result in dose delays or treatment discontinuation, including 33.7% of trastuzumab deruxtecan and 55.5% of sacituzumab govitecan studies discussed by Ballestín et al[2]. Regarding the management of trastuzumab deruxtecan and ado-trastuzumab emtansine, Grade 3 neutropenia generally requires treatment interruption until recovery to Grade 2, followed by continuation at the same dose; Grade 4 neutropenia requires treatment interruption until recovery to Grade 2, followed by resumption at one dose level lower. Similarly, Grade 3-4 anaemia should be

managed by withholding treatment until recovery to Grade 2 and then continuing at a reduced dose, particularly for T-DM1, T-DXd and sacituzumab govitecan. For thrombocytopenia, Grade 3 toxicity requires treatment interruption until recovery to Grade 1, followed by continuation at the same dose, whereas Grade 4 toxicity requires recovery to Grade 1 before resuming treatment at a lower dose.

Sacituzumab govitecan is subject to more specific dose-modification guidelines. For example, Grade 2 neutropenia on Day 1 and Grade 3 neutropenia on Day 8 require treatment interruption until recovery to Grade 1. Other indications for dose modification include a 25% dose reduction at the first incidence, a 50% reduction at the second incidence and treatment discontinuation at the third incidence. These indications include severe neutropenia lasting ≥7 days, febrile neutropenia and treatment delays of 2-3 weeks. Several reviews highlight the need to personalise treatment modifications according to toxicity severity, recurrence, bone marrow reserve and the seriousness of the underlying condition, with a general "hold first, then test" strategy[2,9,22,23].

Dose adjustments for T-DM1, T-DXd and sacituzumab govitecan are summarised according to cytopenia type and toxicity grade. For neutropenia, anaemia and thrombocytopenia, treatment interruption, dose reduction, supportive care and granulocyte colony-stimulating factor (G-CSF)-based strategies are specified according to the severity of the event[2,9] (Table 2).

Growth factor use: Growth factor support is important for the management of neutropenia and for maintaining ADC dose intensity. G-CSF is not routinely recommended for all ADCs, as some agents, such as trastuzumab deruxtecan, are associated with relatively low rates of febrile neutropenia. However, G-CSF may be appropriate for high-risk patients, including those aged >65 years, with advanced-stage cancer, a history of febrile neutropenia, extensive prior treatment, or poor bone marrow reserve. For T-DXd, secondary rather than primary prophylaxis may be considered when Grade 3 neutropenia develops and rapid tumour response or avoidance of treatment delays is clinically important. Short-acting G-CSF may be administered for 2-3 days, or pegylated G-CSF may be administered on Day 2. For sacituzumab govitecan, guidance recommends G-CSF administration following severe neutropenia or febrile neutropenia, with secondary prophylaxis in subsequent cycles. The PRIMED trial recommended short-acting G-CSF during the first two cycles to prevent severe neutropenia; however, this approach is not currently considered standard practice. Literature reviews recognise growth factor support as an accepted strategy for managing persistent or severe cytopenias during treatment, particularly in cases of prolonged bone marrow recovery. In all cases, G-CSF should be used in conjunction with CBC and infection monitoring and in accordance with dose-modification guidelines[22,23].

Supportive care strategies: The ADC-associated haematological toxicity can be managed with transfusions, infection prophylaxis and intensive laboratory monitoring to prevent complications and maintain treatment whenever possible. Red blood cell transfusions are indicated in patients with symptomatic or severe anaemia, whereas platelet transfusions are generally indicated at a platelet count below 10×10^9/L or in patients with bleeding and platelet counts below 50×10^9/L. Iron supplementation should be provided when iron deficiency contributes to anaemia. Because neutropenia is associated with an increased risk of infection, fever should be promptly evaluated to determine its cause and identify any underlying infection. Prophylaxis against opportunistic infections may be necessary in specific situations, particularly in patients receiving prolonged corticosteroid therapy or experiencing combined toxicities with immunosuppressive effects. Educational materials highlight supportive care as a key component of management, with transfusions, antimicrobial therapy and temporary treatment interruption being effective in many cases[22,23].

Recent advances and emerging strategies to mitigate haematological toxicity

Novel linker technologies to improve stability: Linker stability is critical because premature payload release can contribute to myelotoxicity; therefore, improved linker chemistries aim to enhance stability in the bloodstream without compromising intracellular cleavage efficiency. Commonly employed linker systems include enzyme-cleavable peptide linkers (Val-Cit, Val-Ala and Gly-Gly-Phe-Gly), which selectively release the payload through lysosomal protease activity in tumour cells and generally exhibit greater stability than acid-labile hydrazones. The use of self-hydrolysing maleimides and maleimidocaproyl modifications can reduce retro-Michael addition and thereby increase stability *in vivo*, with minimal levels of free payload in circulation. Incorporation of spacers, such as PEG or small hydrophilic linkers, can reduce ADC aggregation and improve circulatory persistence and tolerability, as applied in loncastuximab tesirine and sacituzumab govitecan[1,9,24].

Development of less toxic payloads: Payload selection influences the risk of haematological toxicity. Tubulin binders and DNA-alkylating agents have been associated with myelosuppression and neuropathy and current development strategies increasingly focus on payloads with lower bone marrow toxicity and alternative mechanisms of action. Topoisomerase I payloads, such as deruxtecan and

Table 2. Dose modification guidelines by cytopenia grade

Cytopenia type	ADC(s)	Grade 1/2	Grade 3	Grade 4
Neutropenia	T-DM1/T-DXd	Continue at same dose; monitor complete blood count before each dose	Hold drug until recovery to Grade 2, then resume at the same dose	Hold drug until recovery to Grade 2, then resume at a one-dose-reduced level
Neutropenia	Sacituzumab govitecan (SG)	Grade 2 on Day 1: hold until recovery to Grade 1	Grade 3 (or Grade 3 on Day 8): hold until recovery to Grade 1; if severe (Grade 4 lasting ≥7 days, febrile neutropenia, or delay of 2-3 weeks): 1st occurrence 25% dose reduction+ G-CSF; 2nd occurrence 50% dose reduction+G-CSF; 3rd occurrence discontinue+G-CSF	If neutropenia delays dosing beyond 3 weeks for recovery to Grade 1: discontinue treatment permanently and administer G-CSF (1st occurrence)
Febrile neutropenia	T-DM1/T-DXd/SG	Not applicable at this grade	Hold the drug; for SG, apply the dose-modification schedule above (25%/50% /discontinue) with G-CSF; consider secondary prophylactic G-CSF for subsequent cycles	Same as Grade 3 management; discontinue if recurrent despite dose reduction.
Anemia	T-DM1/T-DXd/SG	Supportive care: evaluate cause of anaemia, iron supplementation (oral or IV), blood transfusion if needed	Hold the drug until recovery to Grade 2, then resume at a one-dose-reduced level	Hold the drug until recovery to Grade 2, then resume at a one-dose-reduced level.
Thrombocytopenia	T-DM1/T-DXd / SG	Continue treatment; monitor platelet counts before each dose	Hold the drug until recovery to Grade 1, then resume at the same dose	Hold the drug until recovery to Grade 1, then resume at a one-dose-reduced level

SN-38, are potent antitumour agents but may still cause neutropenia. Therefore, research is focusing on identifying payloads that are less susceptible to efflux transporters and less prone to systemic distribution, including next-generation topoisomerase inhibitors with reduced affinity for P-glycoprotein (P-gp). Payloads capable of immunomodulation or those that are non-cytotoxic, such as immune agonists and Pattern-recognition Receptor (PRR) agonists in immunostimulatory antibody conjugates (ISACs), are being developed to elicit antitumour responses without directly damaging bone marrow cells. Payloads incorporating prodrug designs and masking strategies, such as enzymatically activated glucuronides or protease-cleavable prodrugs, can minimise the amount of active drug in circulation and consequently reduce haematological toxicity[1,9,25].

Personalised dosing based on pharmacogenomics and therapeutic drug monitoring: Individual patient characteristics and pharmacogenomic factors, including UGT1A1 polymorphisms involved in the metabolism of SN-38, Fc-receptor polymorphisms and genetic variation in transporters and drug-metabolising enzymes, can influence ADC disposition and the risk of haematological adverse effects, supporting the rationale for personalised dosing. In SN-38-based ADCs, including sacituzumab govitecan and related agents, UGT1A1*28 homozygosity has been associated with increased risks of neutropenia and diarrhoea; therefore, genotyping may help identify patients who require closer monitoring or, in selected high-risk cases, dose modification. Therapeutic Drug Monitoring (TDM) and model-informed dosing are complementary strategies that provide opportunities for individualised treatment. Pharmacokinetic/pharmacodynamic (PK/PD) models can help define exposure limits, assess Cmax-related bone marrow toxicity and determine whether adaptive dose or schedule modifications, including dose fractionation, are warranted to avoid high peak exposures that may cause cytopenias. Clinical evidence and hospital series suggest that secondary G-CSF prophylaxis can be guided by observations of the neutrophil nadir and individual patient risk, rather than routine prophylaxis for all patients, thereby maintaining efficacy while minimising haematological events. The combination of pre-treatment genotyping, pharmacokinetic measurements of free drug and total ADC concentrations in plasma and model-informed adaptive dosing represents a personalised treatment approach aimed at reducing severe neutropenia and thrombocytopenia without compromising antitumour efficacy[1,9,24-26].

Future perspectives and research directions: The future of ADC discovery and development is increasingly being shaped by a growing clinical pipeline, which currently

comprises more than 1,300 ongoing trials and targets more than 100 antigens, including established targets such as HER2, TROP2, folate receptor and Nectin-4, as well as emerging targets such as human epidermal growth factor receptor 3 (HER3), B7-H3, CEACAM5, KIT and B7-H4. Various next-generation compounds are in advanced stages of clinical investigation, including datopotamab deruxtecan in Phase III clinical trials compared with conventional chemotherapy in breast cancer. Patritumab deruxtecan, trastuzumab duocarmazine and several other next-generation ADCs are also being evaluated in solid and haematological malignancies. These developments are expected to provide further insight into how linker technology, antigen selection and payload properties can improve therapeutic efficacy while reducing treatment-related toxicity[27,28]

Future developments will depend on the identification of biomarkers that can accurately predict toxicity before the development of clinically significant adverse effects. There is already evidence that patient-specific factors, such as UGT1A1 genotype, play an important role in predicting sacituzumab govitecan-induced neutropenia and diarrhoea. Fc-receptor polymorphisms and antigen heterogeneity may similarly contribute to the prediction of other ADC-related toxicities. Beyond pharmacogenomics, emerging technologies that may enable dynamic assessment include liquid biopsy, Positron Emission Tomography (PET) immunotracers, spatial transcriptomics and single-cell proteomics. These approaches may facilitate real-time assessment of antigen expression and changes within the tumour microenvironment. A major research direction involves rationally combining ADCs with other therapeutic approaches to minimise toxicity while maintaining their tumour-killing potential. Mechanistically based combinations with immune checkpoint inhibitors, PARP inhibitors, Tyrosine Kinase Inhibitors (TKIs), radiation therapy and chemotherapy are under development, not only to enhance efficacy through synergistic effects but also to optimise treatment sequencing, reduce dose requirements and improve patient selection. Notably, some recent studies suggest that sequential combinations may sometimes be more tolerable than concurrent treatment, as observed with sacituzumab govitecan combined with talazoparib. Biomarker-driven combinations may also help avoid overlapping toxicities between treatment modalities, such as neutropenia and thrombocytopenia[29,30].

CONCLUSION

The development of antibody-drug conjugates (ADCs) has been pivotal in the advancement of cancer therapy because it combines the specific targeting properties of monoclonal antibodies with the efficacy of cytotoxic payloads, resulting in enhanced tumour selectivity compared with conventional chemotherapeutic agents. Nevertheless, haematological toxicity remains a critical challenge affecting their therapeutic profile, manifesting as neutropenia, anaemia, thrombocytopenia and in certain cases, febrile neutropenia and haemorrhage. The reviewed literature establishes that haematological toxicities do not depend solely on the type of payload; rather, they arise from the interaction of several factors, including antigen distribution, linker stability, drug-antibody ratio (DAR), internalisation pathways, bystander effects and individual patient susceptibility. Specifically, tubulin inhibitors and high DAR values are associated with the occurrence of haematological toxicities, while linker instability and poor linker design can lead to premature payload release and off-target bone marrow damage. In clinical practice, haematological toxicities can be mitigated through baseline risk assessment, laboratory monitoring, dose adjustment or treatment interruption, administration of growth factors in selected patients and the prompt identification and management of severe toxicities.

Clinically, the broad use of ADCs in both haematological and solid tumours requires standardised toxicity monitoring and multidisciplinary care to maintain therapeutic efficacy while minimising adverse events. From a research perspective, future success will depend on patient selection based on biomarkers, pharmacogenomics, therapeutic drug monitoring and the development of next-generation linkers, less toxic payloads and combination treatment approaches. Thus, mechanistic insight into the haematological toxicities associated with ADCs will be essential for optimising their therapeutic potential while minimising treatment-related toxicity.

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