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Antibody-drug Conjugates in Oncology: A Comprehensive Review of Mechanism, Efficacy, and Toxicity Management

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Abstract

Antibody-drug conjugates (ADCs) represent a transformative advancement in oncology, offering targeted delivery of cytotoxic agents to malignant cells while minimizing damage to healthy tissues; however, their complex mechanism, variable efficacy, and unique toxicity profiles necessitate a comprehensive review to guide clinical practice and future research. This review systematically examines the mechanism of action of ADCs, including antibody specificity, linker stability, and payload potency, evaluates their clinical efficacy across various malignancies such as breast, lung, and gynecologic cancers, and discusses evidence-based strategies for managing ADC-associated toxicities, including hematologic, neurologic, and ocular adverse events. Furthermore, it explores current challenges such as drug resistance and off-target effects, and highlights emerging approaches to optimize ADC design, including novel linkers, payloads, and combination therapies. Future directions emphasize the integration of predictive biomarkers, personalized dosing strategies, and the development of next-generation ADCs to enhance therapeutic precision and improve patient outcomes in oncology.

Keywords: Antibody-drug conjugates, Cancer therapeutics, Efficacy, Mechanism of action, Oncology, Toxicity management, Targeted therapy

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Introduction

The advent of ADCs has revolutionized the landscape of oncology therapeutics, offering targeted delivery of cytotoxic agents to malignant cells while minimizing systemic toxicity [1-5]. A comprehensive understanding of their mechanism, efficacy, and toxicity management is crucial for optimizing clinical outcomes. The current literature provides detailed insights into each of these aspects, highlighting the complexity and potential of ADCs in cancer treatment. Mechanistically, ADCs are composed of a monoclonal antibody linked to a cytotoxic payload via a chemical linker [6-10]. This design enables selective targeting of tumor-associated antigens expressed on cancer cell surfaces, thereby reducing off-target effects [11]. The mechanism of action involves the binding of the ADC to its specific antigen, internalization of the complex, and subsequent release of the cytotoxic payload within the cancer cell, leading to cell death [12-17]. The structural components—antigen specificity, linker stability, and payload potency—are critical determinants of ADC efficacy [18]. Recent advances emphasize the importance of selecting ideal target antigens that are highly expressed on tumor cells but minimally present on normal tissues to enhance selectivity and reduce toxicity [18]. Additionally, innovative strategies such as multitarget approaches, pH-dependent antibodies, and masked peptide technologies are being explored to improve efficacy and safety profiles [19].

Efficacy data from clinical trials underscore the promise of ADCs across various malignancies. For instance, in lung cancer, ADCs have demonstrated significant therapeutic potential, with evidence supporting their role in improving patient outcomes [20]. Similarly, in gynecologic cancers, ADCs like mirvetuximab soravtansine and tisotumab vedotin have received FDA approval based on clinical trial results showing meaningful responses in platinum-resistant ovarian and metastatic cervical cancers, respectively [21]. The efficacy of ADCs is further supported by their ability to deliver potent cytotoxic agents directly to tumor cells, thereby overcoming some mechanisms of resistance associated with traditional chemotherapies [20].

Despite their therapeutic benefits, ADCs are associated with a spectrum of toxicities that necessitate careful management. Toxicity profiles vary depending on the payload, target antigen, and patient-specific factors. Systematic reviews and meta-analyses reveal that ADC-related adverse effects include neurologic, hematologic, ocular, and mucosal toxicities, among others [22]. For example, neurological

adverse events and hematologic toxicities are notable concerns, especially when ADCs are combined with chemotherapy. Ocular toxicities, such as keratopathy and conjunctivitis, are increasingly recognized, particularly in gynecologic oncology settings, where ADCs like those targeting folate receptors have been associated with ocular adverse events [23, 24]. Management strategies for these toxicities involve routine monitoring, prophylactic interventions, and symptomatic treatments tailored to the specific adverse event [23, 25].

Toxicity management also extends to understanding the pharmacokinetics and pharmacodynamics of ADC components. Pharmacokinetic profiles influence dosing strategies and help mitigate adverse effects, especially in patients with organ dysfunction or those receiving concomitant therapies [26]. The importance of personalized approaches is emphasized, with considerations for drug-drug interactions and organ-specific toxicities such as hepatotoxicity, which is a concern with antibody-based therapies, including ADCs [27, 28]. Liver injury, in particular, requires vigilant monitoring and management to balance therapeutic efficacy with safety [27]. The development of resistance remains a significant challenge in ADC therapy. Resistance mechanisms include antigen downregulation, payload efflux, and alterations in intracellular trafficking pathways [18]. Strategies to overcome resistance involve selecting more stable linkers, optimizing payload potency, and identifying new target antigens with higher tumor specificity [18, 19]. Future perspectives focus on integrating biomarkers to predict response and resistance, thereby enabling more personalized treatment regimens [29].

In summary, ADCs represent a potent and targeted approach in oncology, with demonstrated efficacy across multiple cancer types. Their mechanism hinges on precise antigen targeting, efficient internalization, and payload release, which collectively contribute to their therapeutic success. However, toxicity management remains a critical component, requiring ongoing research into adverse effect mitigation strategies, including prophylactic measures and personalized dosing. Advances in target selection, linker technology, and payload design continue to enhance the safety and efficacy profiles of ADCs, promising further integration into standard oncologic care. As research progresses, the combination of ADCs with other modalities and the development of predictive biomarkers are poised to refine their role in precision oncology, ultimately improving patient outcomes.

Mechanism of Action

ADCs represent a significant advancement in oncology, offering a targeted approach to cancer therapy by combining the specificity of monoclonal antibodies with the cytotoxic potency of chemotherapy agents. The mechanism of action of ADCs involves the selective delivery of cytotoxic drugs to cancer cells, thereby minimizing damage to healthy tissues. This targeted approach is achieved through the unique structure of ADCs, which consists of three main components (Table 1): a monoclonal antibody, a cytotoxic drug (payload), and a chemical linker that connects the two [6, 30-34]. The monoclonal antibody specifically binds to antigens expressed on the surface of tumor cells, facilitating the internalization of the ADC and subsequent release of the cytotoxic agent within the tumor cell. This mechanism not only enhances the therapeutic index of the cytotoxic drug but also reduces systemic toxicity. The monoclonal antibody is designed to target specific antigens expressed on cancer cells, allowing for selective delivery of the cytotoxic agent. This targeted approach minimizes off-target effects, enhancing the therapeutic index of the treatment [35, 36]. The linker plays a crucial role in the stability and efficacy of ADCs, as it determines the release mechanism of the cytotoxic drug once the ADC is internalized by the target cell [35]. Linkers can be classified into cleavable and non-cleavable types, with cleavable linkers further categorized into hydrazone, disulfide, and peptide linkers [35].

The monoclonal antibody in ADCs is designed to specifically bind to antigens expressed on the surface of cancer cells. This specificity allows ADCs to target and deliver cytotoxic agents directly to tumor cells, minimizing damage to healthy tissues [37, 38]. The choice of antigen is critical, as it determines the selectivity and effectiveness of the ADC. Ideal target antigens are those that are highly expressed on tumor cells but have limited expression on normal cells [18]. The payload is a highly potent cytotoxic drug that is capable of killing cancer cells upon internalization. Common payloads include microtubule inhibitors (such as auristatins and maytansinoids), DNA-damaging agents, and topoisomerase inhibitors [39]. The potency of the payload is essential because it ensures that even a small amount of drug delivered to the cancer cell can induce cell death, which is crucial for overcoming issues like tumor heterogeneity and resistance [40]. The linker is a chemical moiety that connects the antibody to the cytotoxic drug. It plays a pivotal role in the stability and release of the payload [36]. Linkers can be cleavable or non-cleavable. Cleavable linkers release the drug in response to specific conditions within the tumor microenvironment, such as low pH or the presence of certain enzymes, while non-cleavable linkers require the entire ADC to be internalized and degraded to release the drug [39, 41]. The design of the linker affects the pharmacokinetics and therapeutic index of the ADC, influencing both efficacy and safety [42]. Once the ADC binds to the target antigen on the cancer cell surface, it is internalized into the cell. Inside the cell, the linker is cleaved, releasing the cytotoxic drug [42]. The released drug then exerts its cytotoxic effects, such as disrupting microtubules or damaging DNA, leading to cancer cell apoptosis [43]. This targeted delivery system allows for high concentrations of the drug to be delivered directly to cancer cells, reducing systemic toxicity and improving the therapeutic index [42].

ADCs utilize monoclonal antibodies to specifically bind to the present antigens on the surface of cancer cells. This specificity allows for the selective targeting of tumor cells while sparing normal tissues [36, 44]. Once bound to the target antigen, the ADC is internalized by the cancer cell through endocytosis. The internalized ADC is then trafficked to lysosomes, where the linker is cleaved, releasing the cytotoxic payload into the cell [45, 46]. The cytotoxic payloads used

Table 1: Key components of ADCs and their characteristics.

Component	Role	Types/examples	Critical considerations
Antibody	Targets a specific antigen on the cancer cell surface	Immunoglobulin G (IgG1, IgG4); trastuzumab (anti-HER2), brentuximab (anti-CD30)	High tumor specificity, low normal tissue expression, efficient internalization
Linker	Connects the antibody to the payload; controls payload release	Cleavable: Peptide, hydrazone, disulfide. Non-cleavable: Thioether	Stability in circulation, efficient cleavage in the target cell (e.g., by lysosomal enzymes or low pH)
Payload	Potent cytotoxic agent that kills the cancer cell	Auristatins (Monomethyl auristatin E), maytansinoids (DM1/DM4), topoisomerase I inhibitors (Exatecan derivative for ADC (DXd), SN-38)	High potency (IC_{50} in picomolar-nanomolar range), mechanism of action, and ability to exert bystander effect

in ADCs are highly potent drugs that can induce cell death through various mechanisms, such as DNA damage, microtubule disruption, or inhibition of critical cellular enzymes like topoisomerase [46]. The release of the payload within the tumor cell ensures that the cytotoxic effects are localized, thereby reducing the likelihood of systemic side effects associated with traditional chemotherapy [35, 36]. ADCs can also exert a 'bystander effect,' where the cytotoxic agent diffuses from the targeted cancer cell to neighboring cells, including those with low or no antigen expression. This effect can enhance the overall antitumor activity of ADCs, particularly in heterogeneous tumor environments [35, 46].

Approved ADCs

- Adcetris® (Brentuximab vedotin): Approved for the treatment of CD30-positive Hodgkin lymphoma and systemic anaplastic large cell lymphoma. It utilizes a monoclonal antibody targeting CD30, linked to the cytotoxic agent monomethyl auristatin E via a protease-cleavable linker [47, 48].

- Kadcyla® (Ado-Trastuzumab emtansine): Used for human epidermal growth factor receptor 2 (HER2)-positive breast cancer, this ADC combines trastuzumab with the cytotoxic agent emtansine, linked through a non-cleavable thioether linker. It targets the HER2 receptor, delivering the cytotoxic payload directly to HER2-expressing cancer cells [43, 48].

- Enhertu® (Trastuzumab deruxtecan): Another ADC for HER2-positive breast cancer, it features a novel topoisomerase I inhibitor payload, deruxtecan, linked to trastuzumab. This ADC is noted for its high drug-to-antibody ratio and potent cytotoxicity [49, 50].

- Trodelvy® (Sacituzumab govitecan): Approved for triple-negative breast cancer, it targets the trophoblast cell surface antigen 2 (Trop-2) antigen and delivers the cytotoxic agent 7-ethyl-10-hydroxycamptothecin (SN-38), a topoisomerase I inhibitor [43, 51].

ADCs in development and clinical trials

- Polivy® (Polatuzumab vedotin): Targets CD79b and is used in combination with other therapies for the treatment of diffuse large B-cell lymphoma. It employs the same cytotoxic payload as adcetris, monomethyl auristatin E [47].

- Padcev® (Enfortumab vedotin): Approved for advanced urothelial cancer, it targets nectin-4 and uses monomethyl auristatin E as its cytotoxic payload [49].

- Blenrep® (Belantamab mafodotin): Targets B-cell maturation antigen and is used for multiple myeloma. It delivers the cytotoxic agent mafodotin [47].

Challenges and future directions

- Linker stability and payload potency: The stability of the linker and the potency of the payload are critical for the efficacy and safety of ADCs. Instability can lead to premature release of the cytotoxic agent, causing systemic toxicity [49, 50].

- Target specificity: Identifying tumor-specific antigens is crucial to minimizing off-target effects and improving therapeutic outcomes. The lack of true tumor antigen specificity remains a significant challenge [49].

- Histology-agnostic approaches: There is growing interest in developing ADCs that can target multiple cancer types based on shared molecular markers, rather than histological classification [52].

While ADCs offer a promising approach to cancer therapy, challenges such as resistance and off-target toxicities remain. Ongoing research is focused on improving the design of ADCs, including the development of novel linkers and payloads, to enhance their efficacy and safety . Additionally, the exploration of combination therapies and the identification of predictive biomarkers are critical for optimizing the clinical use of ADCs [53, 54].

Efficacy of ADCs in Oncology

ADCs have shown promising results across various cancer types, including hematologic malignancies and solid tumors. To date, several ADCs have received market approval, with ongoing clinical trials evaluating their efficacy in different settings [36, 55]. For instance, in lung cancer, ADCs targeting antigens such as HER2 and mesenchymal-epithelial transition factors have demonstrated encouraging results, particularly in non-small cell lung cancer [20, 29]. Similarly, in gynecologic cancers, ADCs like tisotumab vedotin and mirvetuximab soravtansine have shown efficacy in treating recurrent or metastatic cases [21, 23]. The mechanism of action of ADCs not only enhances their efficacy but also allows for the exploration of combination therapies. Combining ADCs with immune checkpoint inhibitors or traditional chemotherapy has been a focus of ongoing research, aiming to improve patient outcomes further [20, 29, 55].

ADCs utilize monoclonal antibodies that specifically bind to antigens expressed on cancer cells, allowing for precise targeting and sparing healthy tissues from exposure to cytotoxic agents. This targeted approach significantly reduces the off-target toxicities commonly associated with traditional chemotherapy [42, 56]. The use of stable linkers in ADCs ensures that the cytotoxic payload is released only upon internalization into the cancer cell, further minimizing systemic exposure and associated side effects [57, 58]. ADCs have demonstrated enhanced therapeutic performance by delivering potent cytotoxic agents directly to cancer cells, increasing the likelihood of inducing apoptosis and reducing tumor growth [37, 59]. The incorporation of novel payloads, such as proteolysis targeting chimeras and radioactive isotopes, has expanded the therapeutic arsenal of ADCs, offering new mechanisms to combat cancer cell survival and improve treatment outcomes [60]. By combining the specificity of antibodies with the cytotoxicity of chemotherapy agents, ADCs offer a wider therapeutic window, allowing for higher doses of cytotoxic agents to be delivered directly to cancer cells without increasing systemic toxicity [18]. This broader therapeutic window enhances the safety profile of ADCs, making them suitable for treating a variety of cancers, including those that are difficult to manage with conventional therapies [56, 61].

Linker technologies and payload design are pivotal in optimizing the efficiency of ADCs for oncology applications. These components are integral to the stability, specificity, and therapeutic efficacy of ADCs, which are designed to deliver cytotoxic agents directly to cancer cells while minimizing damage to healthy tissues. The design of linkers and payloads influences the pharmacokinetics, pharmacodynamics, and overall therapeutic index of ADCs, making them crucial for the success of these targeted therapies. Linkers are responsible for maintaining the stability of ADCs in systemic circulation and ensuring the selective release of the payload in the tumor microenvironment. The choice of linkers impacts the pharmacokinetic profile and therapeutic efficacy of ADCs. For instance, cleavable linkers, such as those utilizing protease-cathepsin-cleavable dipeptide sequences, allow for site-

specific activation and bystander killing effects, which are particularly beneficial in solid tumors with heterogeneous antigen expression [62, 63]. Advances in site-specific conjugation methods, such as non-natural amino acid incorporation and enzymatic addition, have improved the precision of linker attachment, enhancing the stability and efficacy of ADCs. These methods help control the antibody-drug ratio and ensure consistent payload delivery [63]. Novel linker technologies, including light-stimulated and chemically reactive linkers, are being explored to provide controlled release mechanisms, potentially increasing the therapeutic window of ADCs [63].

The payloads in ADCs are typically potent cytotoxic agents, such as microtubule inhibitors, DNA-damaging agents, or topoisomerase inhibitors. The choice of payload is critical as it determines the mechanism of action and the potential to exploit disease-specific vulnerabilities. Expanding the repertoire of payloads to include novel mechanisms can enhance the therapeutic efficacy of ADCs [39, 64]. The design of payloads must consider the pathophysiology of the target cancer and the pharmacology of the drug entity. This ensures that the payload is effectively delivered to and acts within the tumor cells, maximizing therapeutic outcomes while minimizing off-target effects [64]. Recent advancements include the development of metal-based and nature-inspired payloads, which offer enhanced selectivity and reduced side effects compared to traditional chemotherapeutic agents. These novel payloads are being integrated into ADCs to improve their clinical efficacy and safety profiles [65].

Several ADCs have received FDA approval for the treatment of various cancers, including hematologic malignancies and solid tumors, underscoring their clinical efficacy and potential to improve patient outcomes [37, 58]. Notable examples include gemtuzumab ozogamicin for acute myeloid leukemia and Ado-trastuzumab emtansine for HER2-positive breast cancer, which have shown significant success in clinical settings [37]. ADCs are designed to limit systemic exposure to cytotoxic agents, thereby reducing common chemotherapy-related side effects such as febrile neutropenia [66, 67]. Despite their targeted nature, ADCs can still cause specific toxicities related to the payload or the immune response. These include potential off-target effects and immunogenicity, which are areas of active research [44]. Meta-analyses have shown that ADCs generally have a more manageable safety profile compared to traditional chemotherapy, although they may not always outperform in terms of objective response rates [67, 68].

While ADCs offer numerous advantages over traditional chemotherapy, challenges such as drug resistance and the development of adverse effects remain. Resistance mechanisms, including antigen heterogeneity and impaired internalization, can limit the effectiveness of ADCs. Addressing these challenges through combination therapies and personalized treatment strategies may further enhance the clinical efficacy of ADCs. Additionally, ongoing research into optimizing ADC design and identifying novel target antigens continues to hold promise for expanding their therapeutic applications in cancer treatment [18, 69].

Toxicity Management

Despite their targeted nature, ADCs are associated with unique toxicity profiles that can impact patient quality of life and treatment adherence. Common adverse effects include fatigue, nausea, and hematologic toxicities such as thrombocytopenia and elevated liver enzymes [21, 22, 55]. A systematic review highlighted that patients treated with ADCs had a higher risk of certain all-grade toxicities compared to those receiving other anticancer agents, although they exhibited a lower risk of febrile neutropenia [22]. Management of ADC-related toxicities requires a multidisciplinary approach. Strategies include routine monitoring of liver function, dose modifications, and supportive care measures to address specific adverse events such as oral mucositis and ocular toxicities [24, 25]. For instance, ocular toxicities associated with ADCs in gynecologic oncology have prompted the development of preventive and management protocols to mitigate their impact on patient quality of life [23, 24].

Modulating the pharmacokinetics of ADCs can reduce toxicity. For example, incorporating polyethylene glycol chains into the drug-linker can alter the clearance rate of ADCs, potentially reducing tissue exposure to the cytotoxic payload [70]. Faster clearing ADCs have been associated with higher early tissue concentrations of the cytotoxic drug, leading to increased toxicity. Therefore, optimizing the clearance rate is a strategy to enhance tolerability [70]. Despite advancements, ADCs still face challenges related to their toxicity profiles. Many ADCs fail in clinical development due to excessive toxicities, and even approved ADCs often require dose reductions or treatment discontinuations (Table 2) [71]. Continued research is needed to develop next-generation ADCs with improved safety profiles. This includes designing more stable linkers, selecting appropriate payloads, and employing combination therapies to enhance efficacy while minimizing toxicity [72].

Current clinical management strategies

- Dose modifications: Dose delays and reductions are common strategies to manage ADC-related toxicities. These modifications help mitigate adverse effects while maintaining therapeutic efficacy. For instance, ocular toxicities, which are prevalent with ADCs, often improve with dose adjustments [73].

- Supportive care: The use of supportive medications such as artificial tears, topical steroids, and vasoconstrictors is recommended for managing ocular adverse events. Similarly, prophylactic measures and supportive medications are employed to address systemic toxicities like neutropenia, nausea, and diarrhea [74].

- Multidisciplinary approach: Effective management of ADC toxicities requires collaboration among oncologists, ophthalmologists, and other healthcare professionals. This approach ensures comprehensive monitoring and timely intervention, particularly for complex adverse events like ocular toxicities [73].

Table 2: Common ADC-related toxicities and management strategies.

Toxicity type	Common manifestations	Associated ADC(s)	Management strategies
Hematologic	Neutropenia, thrombocytopenia, anemia	Common across many ADCs (e.g., T-DM1, T-DXd)	Dose delays/reductions, growth factor support, transfusions
Ocular	Keratopathy, dry eye, conjunctivitis	Belantamab mafodotin, tisotumab vedotin	Prophylactic steroid/vasoconstrictor eye drops, regular ophthalmologic exams, dose modifications
Neurologic	Peripheral sensory neuropathy	Brentuximab vedotin, enfortumab vedotin	Dose adjustment, gabapentin/pregabalin, symptomatic management
Pulmonary	Interstitial lung disease	Trastuzumab deruxtecan	Immediate corticosteroid therapy, permanent discontinuation
Gastrointestinal	Nausea, vomiting, diarrhea	Sacituzumab govitecan, others	Prophylactic antiemetics, antidiarrheals, fluid/electrolyte support

- Monitoring protocols: Regular monitoring of patients for early signs of toxicity is crucial. This includes routine blood tests and clinical assessments to detect and manage adverse events promptly, thereby preventing severe complications [74].

Influence of physicochemical properties on toxicity

- Drug-to-antibody ratio: Higher drug-to-antibody ratios can increase the potency of ADCs but may also lead to increased toxicity due to higher systemic exposure to the cytotoxic payload. Balancing drug-to-antibody ratio is crucial to maintain efficacy while minimizing adverse effects [70, 75].

- Linker stability: The stability of the linker affects the release of the cytotoxic drug. Unstable linkers may lead to premature drug release, causing off-target toxicity. Conversely, overly stable linkers may reduce drug release at the target site, decreasing efficacy [72].

- Payload properties: The inherent toxicity of the payload is a major determinant of ADC safety. Payloads with high potency can cause significant off-target effects if not adequately controlled by the antibody targeting mechanism [11, 71].

Strategies to optimize ADC safety

- Linker optimization: Developing linkers that are stable in circulation but cleavable in the tumor microenvironment can reduce systemic toxicity. This approach ensures that the payload is released primarily at the target site [76].

- Antibody engineering: Enhancing the specificity and affinity of the antibody for the target antigen can reduce off-target binding and associated toxicities. This includes using pH-dependent antibodies and masked peptide technologies to improve targeting precision [19, 36].

- Pharmacokinetic modulation: Adjusting the pharmacokinetics of ADCs through modifications such as PEGylation can influence drug clearance rates, potentially reducing tissue exposure to the cytotoxic payload and improving tolerability [70].

- Combination therapies: Combining ADCs with other therapeutic agents can enhance efficacy and allow for lower doses of ADCs, potentially reducing toxicity. However, this approach requires careful management to avoid additive toxicities [11].

While ADCs offer a targeted approach to cancer therapy, their associated toxicities present significant challenges. Effective management requires a comprehensive understanding of the mechanisms of toxicity, implementation of risk minimization strategies, and optimization of pharmacokinetics. Ongoing research and development are essential to improve the safety and efficacy of ADCs, ensuring they can fulfill their potential as a cornerstone of cancer treatment.

Clinical Studies

ADCs have emerged as a promising class of targeted cancer therapies, combining the specificity of monoclonal antibodies with the potent cytotoxic effects of chemotherapy agents. Over the past two decades, ADCs have gained significant traction in oncology, with numerous clinical trials exploring their efficacy across various cancer types. As of December 31, 2022, 431 clinical trials have been initiated to study ADCs for cancer treatment, with a significant increase in the number of trials over the last decade compared to the previous one. These trials cover a wide range of cancer indications, including breast cancer, lymphoma, bladder cancer, and lung cancer, with breast cancer and lymphoma being the most frequently studied. ADCs target specific antigens, with erythroblastic oncogene B 2(HER2) and tumor necrosis factor receptor superfamily member 8 (CD30) being the most common targets, involved in over 100 registered clinical trials each [77].

The Children's Oncology Group trial AAML0531 investigated [78] the efficacy of gemtuzumab ozogamicin in treating newly diagnosed acute myeloid leukemia in children and adolescents, focusing on event-free survival (EFS) and overall survival (OS), as well as outcomes by risk group and intensification method. The trial enrolled 1,070 patients aged 1 month to 29.99 years with newly diagnosed primary acute myeloid leukemia between August 2006 and June 2010. After exclusions, 1,022 evaluable patients were included in the analysis. Patients were randomly assigned to either standard five-course chemotherapy alone (No-gemtuzumab ozogamicin arm) or the same chemotherapy regimen with two doses of gemtuzumab ozogamicin (3 mg/m^2/dose) administered during induction course 1 and intensification course 2. Gemtuzumab ozogamicin significantly improved EFS (3-year EFS: 53.1% vs 46.9%; hazard ratio (HR), 0.83; 95% confidence interval (CI), 0.70 to 0.99; p = 0.04). However, gemtuzumab ozogamicin did not significantly improve OS (3-year OS: 69.4% vs 65.4%; HR, 0.91; 95% CI, 0.74 to 1.13; p = 0.39). Post-hoc analyses revealed a significant reduction in relapse risk among gemtuzumab ozogamicin recipients overall (3-year relapse risk: 32.8% vs 41.3%; HR, 0.73; 95% CI, 0.58 to 0.91; p = 0.006). This improvement was qualitatively similar across all risk groups. Despite the reduced relapse risk, there was an increased postremission toxic mortality in the gemtuzumab ozogamicin arm (3 years: 6.6% vs 4.1%; HR, 1.69; 95% CI, 0.93 to 3.08; p = 0.09). This was particularly noted in low-risk patients and associated with prolonged neutrophil recovery times during intensification course 2. Disease-free survival was better among gemtuzumab ozogamicin recipients (3 years: 60.6% vs 54.7%; HR, 0.82; 95% CI, 0.67 to 1.02; p = 0.07). Remission rates were not significantly improved by gemtuzumab ozogamicin (88% vs 85%; p = 0.15). The study concluded that adding gemtuzumab ozogamicin to chemotherapy improved EFS in children and adolescents with acute myeloid leukemia by reducing the risk of relapse. These findings are consistent with recent adult randomized controlled trials and support the use of anti-CD33 ADCs in acute myeloid leukemia treatment. In summary, the AAML0531 trial demonstrated that gemtuzumab ozogamicin significantly improved EFS and reduced relapse risk in pediatric acute myeloid leukemia patients, although it did not lead to a statistically significant improvement in OS and was associated with increased post remission toxic mortality.

A study by Zhao et al. [79] (NCT01564784) reported efficacy of inotuzumab ozogamicin (InO) in relapsed/refractory acute lymphoblastic leukemia (Figure 1). InO demonstrated superior outcomes compared to standard of care chemotherapy in adult patients with relapsed/refractory acute lymphoblastic leukemia during phase 3 InO trial to investigate tolerability and efficacy (INO-VATE) trial. Patients receiving InO showed higher rates of remission, improved measurable residual disease negativity, and enhanced OS. Out of 326 random patients in the INO-VATE trial, 91 had samples available for genomic analysis (43 in the InO group and 48 in the standard of care chemotherapy group). The types of gene fusions and other genomic alterations observed in these patients were consistent with findings from previous studies on adult acute lymphoblastic leukemia. Responses to InO were observed across all leukemic subtypes, various genomic alterations, and different risk groups, indicating broad potential benefit. InO led to significantly higher rates of complete remission (CR)/CR with incomplete recovery compared to standard

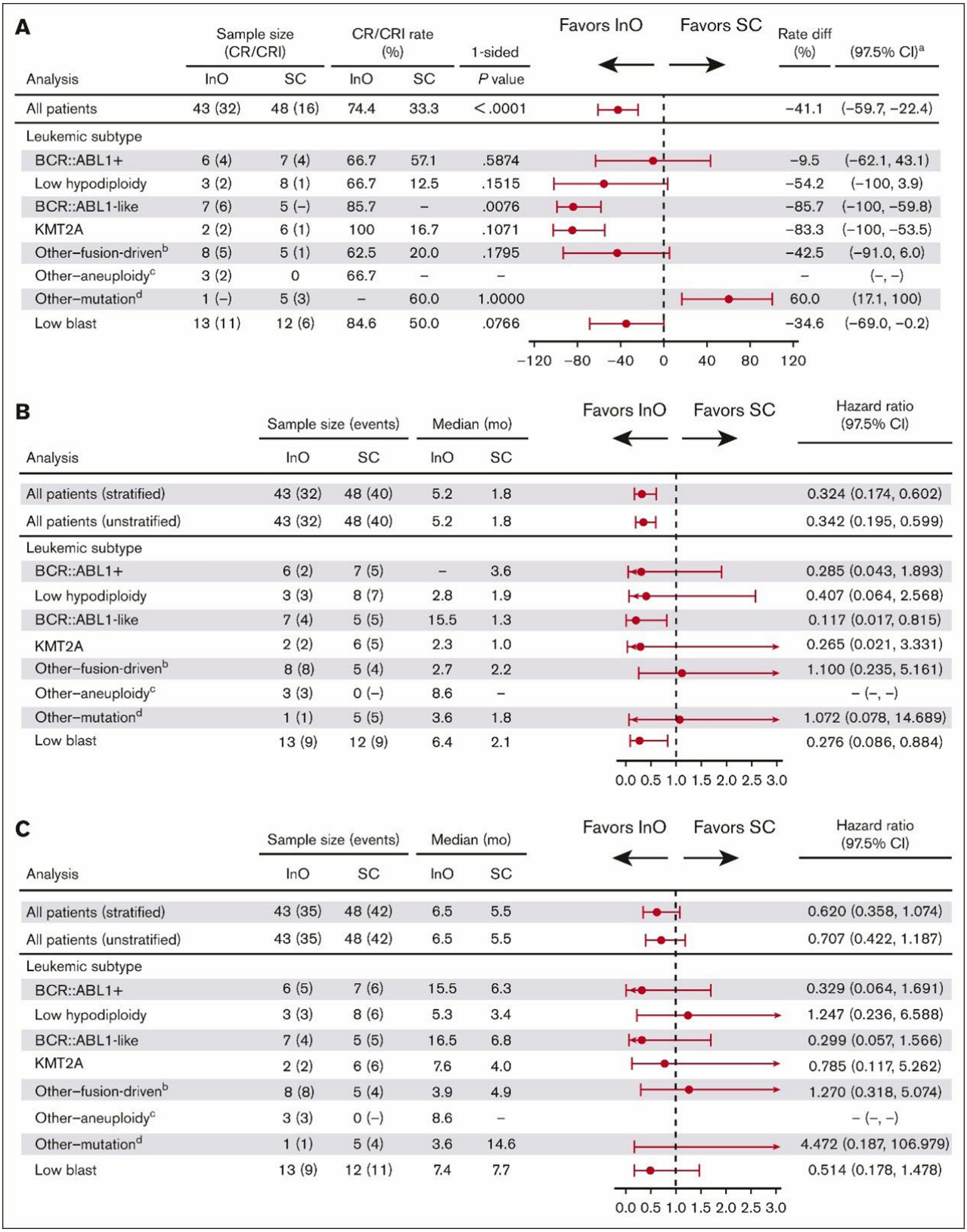

Figure 1: Efficacy results for InO vs standard of care chemotherapy by acute lymphoblastic leukemia subtypes are shown. **(A)** Compared to standard of care chemotherapy, InO produced higher CR/CRi rates in all subtypes, with a statistically significant difference in the BCR:ABL1–like group; **(B)** A PFS benefit favoring InO was observed across subtypes; and **(C)** an OS benefit was seen in most subtypes. [a] refers to confidence intervals that were approximated using the nominal distribution if there were ≥5 patients in both response subgroups; if not, the exact method was used; [b] is the indicated group which includes DUX4, CDX2/UBTF, MEF2D, TCF3:PBX1, and ZNF384; [c] refers to the hyper diploid subtype; and [d] includes B-other, PAX5alt, and ZEB2/CEBP [79].

of care chemotherapy in specific patient subgroups: BCR::ABL1-like acute lymphoblastic leukemia:InO achieved an 85.7% (6/7) CR/CRi rate, whereas standard of care chemotherapy had 0% (0/5) ($p = 0.0076$). Patients with tumor suppressor gene (TP53) alterations treated with InO had a 100% (5/5) CR/CRi rate, compared to 12.5% (1/8) with standard of chemotherapy ($p = 0.0047$). For the high-risk group (comprising BCR::ABL1-like, low hypodiploid, and KMT2A-rearranged ALL), InO showed an 83.3% (10/12) CR/CRi rate, significantly higher than the 10.5% (2/19) observed with standard of care chemotherapy ($p < 0.0001$). This retrospective, exploratory analysis suggests that InO holds potential benefits for relapsed/refractory acute lymphoblastic leukemia patients across various leukemic subtypes, including BCR::ABL1-like acute lymphoblastic leukemia, and those with diverse genomic alterations. Further confirmation of InO efficacy is particularly warranted for patients with the BCR::ABL1-like subtype or harboring TP53 alterations. In summary, the study highlights the effectiveness of InO in treating relapsed/refractory acute lymphoblastic leukemia, especially in patient populations with specific high-risk molecular profiles, demonstrating a clear advantage over standard chemotherapy.

A study by Hoimes et al. [80] investigated the combination of enfortumab vedotin and pembrolizumab in previously untreated, cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer (Figure 2). A total of 45 patients received enfortumab vedotin plus pembrolizumab combination therapy. The most frequently observed treatment-related adverse events (TRAEs) included peripheral sensory neuropathy (55.6%), fatigue (51.1%), and alopecia

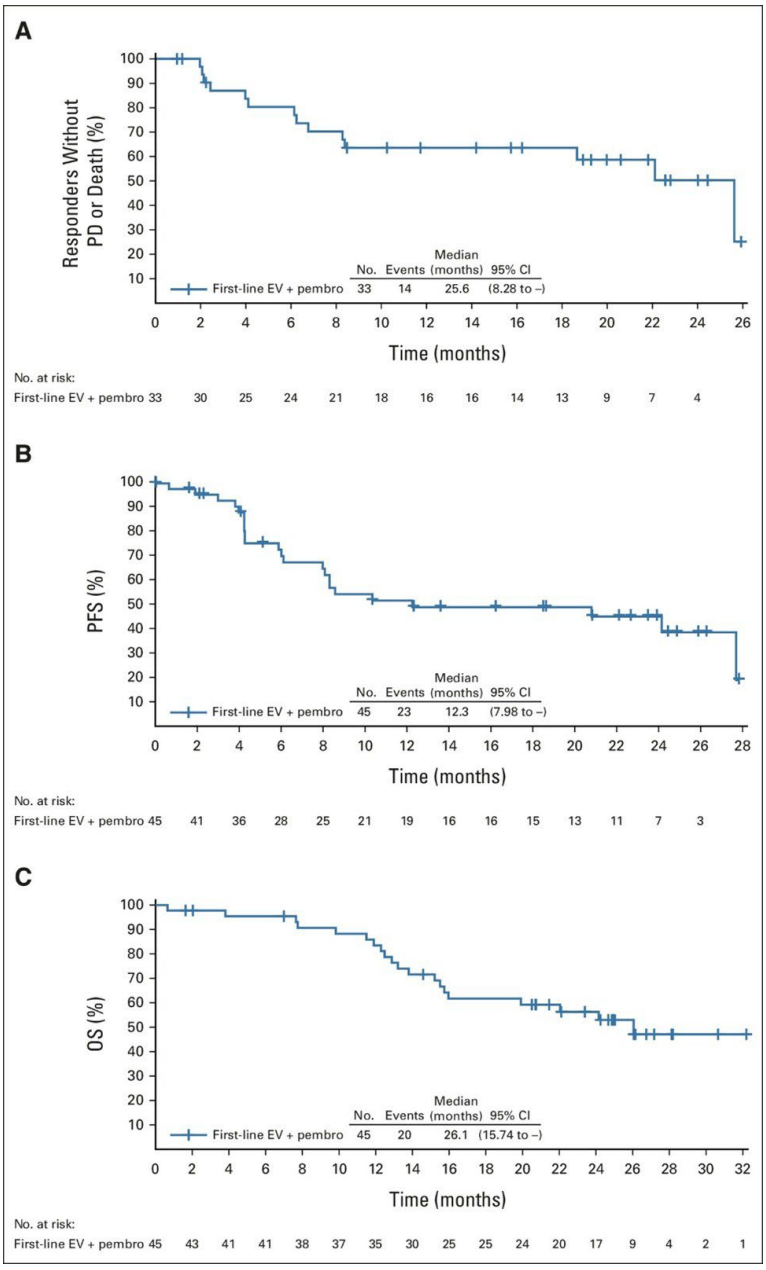

Figure 2: (A) Duration of response, **(B)** PFS, and **(C)** OS as assessed by the investigator using RECIST v1.1 criteria [80].

(48.9%). Twenty-nine patients (64.4%) experienced grade 3 or higher TRAEs. The most common among these were increased lipase (17.8%), maculopapular rash (11.1%), and fatigue (11.1%). One death (2.2%) was classified as a TRAE. The confirmed objective response rate was 73.3% after a median of 9 cycles. A complete response was observed in 15.6% of patients. The median duration of response was 25.6 months. The median OS was 26.1 months. In conclusion, the combination of enfortumab vedotin and pembrolizumab demonstrated a manageable safety profile and significant efficacy, with a high objective response rate and a median duration of response and OS exceeding two years in a cisplatin-ineligible patient population. These promising results have led to its further investigation in a phase III study.

While ADCs have shown transformative potential in oncology, their clinical application is not without challenges. The complexity of ADCs, including their interaction with the tumor microenvironment and the need for precise targeting, necessitates ongoing research and development. The future of ADCs in cancer therapy will likely involve a combination of innovative engineering, strategic clinical trial design, and personalized medicine approaches to maximize their therapeutic potential.

Challenges and Future Directions

The design and optimization of ADCs in oncology face several challenges, primarily related to improving efficacy and reducing toxicity. ADCs are complex molecules that combine the specificity of monoclonal antibodies with the potency of cytotoxic drugs, aiming to deliver targeted cancer therapy. Despite their potential, the development of ADCs is hindered by issues such as off-target toxicity, drug resistance, and the need for precise drug-to-antibody ratios. Future directions in ADC development focus on addressing these challenges through innovative design strategies and technological advancements.

Key challenges

- Toxicity management: ADCs often cause significant side effects, including hematologic, ocular, skin, and neurological toxicities, which limit their clinical application. These toxicities arise from both targeted and off-target effects, necessitating strategies to improve ADC safety by optimizing antibody structure, effector molecules, and linkers [72].

- Drug-to-antibody ratio heterogeneity: The therapeutic efficacy of ADCs is compromised by variability in drug-to-antibody ratio, which affects both cytotoxicity and pharmacokinetics. Achieving a homogeneous drug-to-antibody ratio is crucial for consistent therapeutic outcomes [81].

- Target selection and resistance: Selecting appropriate targets is critical for ADC efficacy. Resistance mechanisms, such as antigen downregulation and drug efflux, pose significant challenges. Strategies to overcome resistance include the use of multi-specific drugs and advanced target selection technologies [19].

Future directions

- Innovative payloads and linkers: The integration of novel payloads, such as immune-stimulating agents, natural toxins, and radionuclides, can enhance therapeutic efficacy and specificity. Additionally, advancements in linker technology can improve the stability and release profile of the cytotoxic payload [60, 82].

- Bioconjugation and analytical techniques: Recent advances in bioconjugation platforms and analytical techniques are shaping the future development of ADCs. These technologies enable more precise conjugation processes and better characterization of ADCs, leading to improved product quality and safety [47].

- Combination therapies: Combining ADCs with other therapeutic modalities, such as immunotherapy, can enhance their efficacy and expand their therapeutic window. This approach may also help mitigate resistance and improve patient outcomes [11].

- Advanced targeting strategies: The use of bispecific antibodies and pro-body-drug conjugates offers promising strategies for improving ADC targeting and minimizing off-target effects. These innovations are crucial for enhancing the precision and effectiveness of ADCs in cancer therapy [11].

- Improving ADC tolerability: Research is focused on understanding the mechanisms of ADC toxicity to develop strategies that enhance tolerability. This includes exploring site-specific conjugation chemistry and preventing normal tissue binding to reduce off-target effects [75].

- Innovative ADC designs: Future ADCs may incorporate novel linker technologies and payloads to improve targeting specificity and reduce systemic exposure. These advancements could potentially lower the incidence of dose-limiting toxicities [71, 75].

- Personalized therapy approaches: Tailoring ADC therapy based on individual patient profiles and tumor characteristics is a promising area of research. This precision medicine approach aims to optimize the balance between efficacy and safety [83].

- Cross-disciplinary research: Collaboration between different scientific disciplines is essential to develop new strategies for managing ADC-related adverse events. This includes integrating insights from immunology, pharmacology, and oncology [73].

While ADCs hold great promise in oncology, their development is fraught with challenges that require ongoing research and innovation. The integration of novel technologies and strategies, such as advanced targeting methods and combination therapies, is essential for overcoming these hurdles and realizing the full potential of ADCs in cancer treatment. However, the complexity of ADCs and the intricacies of their mechanisms of action necessitate a careful balance between efficacy and safety, underscoring the importance of continued optimization efforts in this rapidly evolving field.

Conclusion

Mechanistic insights elucidate that the structural elements of ADCs—the antibody specificity, linker stability, and payload potency—critically influence therapeutic outcomes, bystander killing effects, and resistance development. Resistance to ADCs is multifactorial, involving antigen loss or downregulation, impaired internalization, payload efflux, and tumor microenvironment factors, which collectively challenge durable responses. Emerging strategies to surmount resistance include structural optimization of ADC components, biomarker-driven patient selection, and deployment of novel payloads such as peptide-drug conjugates and immune-stimulating agents. Despite promising early-phase data, many innovative ADC constructs require further clinical validation.

Safety profiles of ADCs are generally manageable and distinct from traditional chemotherapy, with common adverse events including fatigue, nausea, sensory neuropathy, and hematologic toxicities. Specific

targets impart unique toxicity risks, such as cardiac events with HER2-directed ADCs and hemorrhagic complications linked to tissue factor targeting. Combination of regimens integrating ADCs with immune checkpoint inhibitors or chemotherapy agents have demonstrated enhanced efficacy and progression-free survival (PFS) gains but require vigilant toxicity management due to increased adverse event incidence. Long-term safety data remain limited, underscoring the necessity for ongoing pharmacovigilance.

The literature converges to affirm that ADCs represent a transformative advancement in oncology, significantly improving OS and PFS across a range of solid and hematologic malignancies. Breast cancer, particularly HER2-positive and triple-negative subtypes, emerges as the leading area where ADCs have demonstrated the most pronounced therapeutic benefits. Notably, next-generation ADCs such as trastuzumab deruxtecan and sacituzumab govitecan have shown superior efficacy in prolonging survival and enhancing objective response rate compared to conventional chemotherapies or earlier ADCs. Additionally, ADCs targeting emerging antigens like Trop-2, CLDN18.2, and nectin-4 have expanded their clinical utility into gastric, urothelial, lung, ovarian, and prostate cancers, confirming their broad oncologic relevance.

Methodological heterogeneity among clinical trials, including variable endpoints, patient populations, and comparator arms, complicates direct comparative efficacy assessments across ADCs and cancer types. Moreover, underrepresentation of older adults and biomarker assay variability limit the generalizability of findings and precise patient stratification. Real-world studies reinforce clinical trial results but highlight outcome variability linked to patient characteristics and treatment sequencing.

In conclusion, the literature crystallizes ADCs as a pivotal and rapidly advancing class of targeted cancer therapeutics with demonstrated clinical benefit and acceptable safety across multiple malignancies. Nonetheless, optimizing their therapeutic index demands continued research into resistance mechanisms, biomarker refinement, combination strategies, and novel payload development. These efforts are essential to personalize ADC therapy, enhance efficacy, mitigate toxicity, and ultimately improve patient outcomes in oncology.

Acknowledgments

None.

Conflict of Interest

None.

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