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Review Article

Antibody-Drug Conjugate in the Treatment of Pediatric AML and ALL: A Review

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Abstract: Purpose: Antibody-drug conjugate has certain advantages in the treatment of childhood leukemia, which can improve the therapeutic effect and reduce toxic side effects. In this review, we try to collect all available human and pre-clinical data from 2021 to 2023 in this field. Methods: The search was done in PubMed database, using the following keywords: "Leukemia," "Inotuzumab ozogamicin," "Gemtuzumab ozogamicin," "Antibody drug conjugate," "Pediatric," "Children," "Childhood," In vitro studies, animal studies or clinical studies focusing solely on pharmacokinetics, pharmacoeconomics or safety were discarded. This review focuses on clinical outcomes including the assessment of complete response rate, adverse drug reactions and event free survival. Other clinical outcomes taken into account were adjunctive medications, relapse or motality. Results: Based on 16 included studies in this review, the vast majority of patients achieved hematologic remission with ADC therapy. The adverse reactions caused by ADC recorded in all studies include: neutropenia with fever, gastrointestinal symptoms, VOD, cytokine syndrome, infection, sepsis, gastrointestinal symptoms, hyperglycemia, hyperphosphatemia, anemia, thrombocytopenia, tumor lysis syndrome, liver function damage, altered mental state and abdominal swelling. Conclusion: Further studies are required to determine the optimal dose, duration, and the best formulation of ADC to prevent and/or manage chemotherapy-induced complications.

Keywords: Antibody-Drug Conjugate, Leukemia, Gemtuzumab Ozogamicin, Inotuzumab Ozogamicin, Adverse Reactions

1. Introduction

Childhood leukemia is a term that encompasses a group of malignant hematopoietic stem cell disorders that affect children and adolescents under 18 years of age. The main types of childhood leukemia are acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) [1]. Childhood leukemia is the most common pediatric cancer, representing one-third of all malignancies in children. It has an annual incidence of about 300,000 cases worldwide, with 80% being ALL and 20% being AML [2]. The etiology of childhood leukemia remains elusive, but it may involve genetic, environmental, infectious and other factors [3]. The clinical manifestations of childhood leukemia vary widely, but they typically include anemia, bleeding, fever, infection, bone marrow suppression and extramedullary infiltration. The diagnosis of childhood leukemia depends on bone marrow smear, immunophenotyping, cytogenetics and molecular biology tests [4]. The treatment of childhood leukemia mainly consists of chemotherapy, radiotherapy, immunotherapy and hematopoietic stem cell transplantation [5]. In recent years, the molecular mechanisms and biomarkers of childhood leukemia have been elucidated more deeply, and new drugs and treatment protocols have been developed continuously. These advances have led to a significant improvement in the treatment outcome of childhood leukemia, with a 5-year survival rate exceeding 80% [6]. However, some patients still fail to respond or develop resistance to standard chemotherapy regimens, or experience severe toxic side effects

and complications during treatment, resulting in poor prognosis [7, 8]. Therefore, finding more effective, safer and personalized treatment strategies is an important goal and challenge in the field of childhood leukemia therapy.

Table 1. *Clinical characteristics utilizing ADCs for acute leukemia in children.*

No.	Reference	Study design	Location	Study population	Age
1	PMID: 34048275	RCT	USA	AML patients	0-18y
2	PMID: 30093401	RCT	Germany	AML patients	0-18y
3	PMID: 26786921	RCT	USA	AML patients	0-18y
4	PMID: 31113932	RCT	USA	AML patients	0-29y
5	PMID: 28644774	RCT	USA	AML patients	0-29
6	PMID: 36031729	Case Reports	USA	ALL patients	5y
7	PMID: 33512872	Case Reports	Japan	ALL patients	14y
8	PMID: 29734213	Case Reports	USA	EML patients	5 & 7y
9	PMID: 35200224	Case Reports	USA	AML patients	23m & 3y
10	PMID: 30807395	Case Reports	USA	ALL patients	7y
11	PMID: 35091516	Case Reports	Japan	APL patients	8m
12	PMID: 30485640	Case Reports	Spain	ALL patients	14y
13	PMID: 34001796	Case Reports	Japan	ALL patients	11y
14	PMID: 33619887	Case Reports	Japan	ALL patients	11y
15	PMID: 31189528	Case Reports	Japan	ALL patients	16y
16	PMID: 31189528	Case Reports	USA	ALL patients	7y

Table 1. *Continued.*

No.	Medicine	Treatment outcome	ADR	Adjunctive medications
1	GO	KMT2A rearrangement patients CR:77% (GO, n=108) vs 64% (No-GO, n=107) EFS:48±6% (GO, n=108) vs 29±6% (no-GO, n=107)	-	Cytarabine, daunorubicin
2	GO	4 years OS:18±5%(GO, n=76)	49 cases of grade 3-4 infection or neutropenia with fever (69%), 2 cases of sepsis, 11 cases of gastrointestinal symptoms, 7 cases of infusion related reactions, 2 cases of VOD, and 1 case of cytokine syndrome	Fludarabine, cytarabine, daunorubicin
3	GO	EFS:65±6% (GO, n=361 vs 58±6% (no-GO, n=296)	-	Cytarabine, daunorubicin
4	GO	5 years EFS ABCB1 rs1045642 GO Group:CC = 44±9% (n=128), CT = 55±7% (n=238), TT = 56±10 % (n=102); no-GO Group:CC=50±9% (n=132), CT=44±6% (n=244), TT=48±11% (n=93) ABCB1 rs2235015 GO Group:GG = 52±8% (n=294), GT = 55±8% (n=141), TT = 37±19% (n=27); no-GO Group:GG=46±6%(n=300), GT=49±9% (n=141), TT=41±20% (n=24)	-	Cytarabine, daunorubicin
5	GO	5 years EFS 53±5% (GO, n=408) vs 46±5% (no-GO, n=408)	-	Cytarabine, daunorubicin
6	IO	CR, MRD < 1×10^{-4}	Grade1 hyperglycemia, grade 1 cytokine release syndrome, grade 2 hyperphosphatemia, grade 3 anemia, grade 4 thrombocytopenia, grade 4 neutropenia, grade 1 anemia	Cyclophosphamide, vincristine, dexamethasone, rituximab, belintoximab, methotrexate, cytarabine
7	IO	CR, MRD < 1×10^{-4}	Fever induced neutropenia (CTCAE level 3) and tumor lysis syndrome (CTCAE level 3)	Cytarabine
8	GO	Both Dead		Cytarabine, Decitabine
9	GO	CR, MRD < 1×10^{-3}	Respiratory distress, hypotension, altered mental state, and abdominal swelling	Anthracycline
10	IO	relapse	Fever and appendicitis	Methylprednisolone, acetaminophen, diphenhydramine, ursodeoxycholic acid
11	GO	CR, MRD < 1×10^{-3}	Febrile neutropenia	ATRA, ATO, and cytarabine
12	IO	CR, MRD < 1×10^{-4}	-	-
13	IO	CR, MRD > 1×10^{-4}	-	Blinatumomab
14	IO	CR, MRD < 1×10^{-4}	-	-
15	IO	CR, MRD < 1×10^{-4}	Grade 1 liver function damage,	-

No.	Medicine	Treatment outcome	ADR	Adjunctive medications
16	IO	Dead	thrombocytopenia -	Blinatumomab

RCT, randomised controlled trial; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CR, complete relief; MRD, measurable residual disease; EML, extramedullary leukemia; APL, acute promyelocytic leukemia; IO, inotuzumab ozogamicin; GO, gemtuzumab ozogamicin; ATRA, all-trans retinoic acid; ATO, arsenic trioxide; EFS, event free survival.

Antibody-drug conjugates (ADCs) are a novel class of targeted therapy drugs that comprise monoclonal antibodies that specifically recognize tumor-associated antigens and cytotoxic drugs that effectively kill tumor cells through stable linkers [9]. ADCs leverage the high affinity and selectivity of monoclonal antibodies to deliver cytotoxic drugs to the surface of tumor cells, and enter tumor cells via endocytosis. In lysosomes, cytotoxic drugs are released to achieve specific killing of tumor cells while minimizing damage to normal tissues [10]. ADCs have the following advantages: (1) they improve the therapeutic index of cytotoxic drugs, that is, they increase their concentration and duration of action in tumor tissues and decrease their concentration and duration of action in normal tissues; (2) they expand the types of cytotoxic drugs available for treatment, that is, they can use some conventional cytotoxic drugs as well as some novel cytotoxic drugs such as calicheamicin, duocarmycin and maytansine; (3) they enhance the effect of cytotoxic drugs by synergistic action through multiple pathways such as monoclonal antibody immune effect, cytotoxic drug direct effect and tumor microenvironment improvement; (4) they achieve personalized treatment by selecting the most suitable ADCs according to the expression level and distribution characteristics of tumor-associated antigens in different patients, improving efficacy and safety [11-15].

In recent years, ADCs have been increasingly used in the treatment of childhood leukemia. Several ADCs have been approved or licensed for clinical trials by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA), targeting different immunophenotypes and molecular markers. They have demonstrated promising clinical efficacy and safety. This article aims to review the application progress of ADCs in the treatment of childhood ALL and AML, analyze their advantages and limitations as well as challenges and problems encountered by them, and provide new insights and directions for childhood leukemia therapy.

2. Method

Eligible studies should involve the administration of instilled inotuzumab ozogamicin or gemtuzumab ozogamicin, either as monotherapy or combination therapy. Studies referring to the administration of inotuzumab ozogamicin or gemtuzumab ozogamicin were included only if the patients were under 18 years old (one was under 29y) and diagnosed with acute lymphocytic leukemia or acute myeloid leukemia. Eligible studies were required to present clinical outcomes related to the use of ADC therapy.

Eligible studies should be written in the English language and be original research articles. Study design as well as date and place where it was conducted were not taken into account. Reviews, editorials, conference abstracts and textbook chapters were excluded. In vitro studies, animal studies or clinical studies focusing solely on pharmacokinetics, pharmacoeconomics or safety were discarded. This review focuses on clinical outcomes including the assessment of complete response rate, adverse drug reactions and event free survival. Other clinical outcomes taken into account were adjunctive medications, relapse or motality.

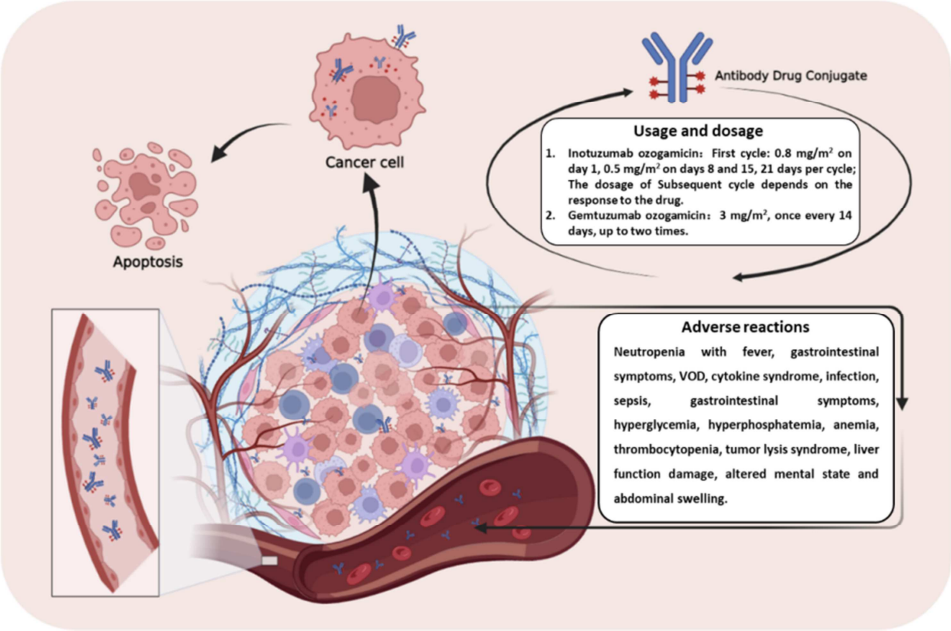

Figure 1. *Molecular mechanism diagram of ADC.*

3. Mechanism of Antibody-Drug Conjugates

Antibody-drug conjugate is a novel type of anti-tumor biologics that consist of three components: a monoclonal antibody that targets tumor cell antigens, a linker that connects the antibody and the payload, and a small molecule cytotoxic drug [16]. As shown in Figure 1, the molecular mechanism of ADCs is to bind to specific antigens on the surface of tumor cells through antibodies, then be internalized by cells, and finally release cytotoxic drugs in lysosomes, thereby killing tumor cells [17]. The advantage of ADCs is that they can improve the targeting and killing efficiency of drugs, while reducing the toxic side effects on normal tissues.

The design of ADCs requires considering the selection and optimization of each component, including antibody, linker, drug and conjugation method. The selection of antibodies requires high affinity, specificity and internalization rate, and can recognize antigens that are highly expressed on the surface of tumor cells and lowly or not expressed in normal tissues [18]. The selection of linkers requires good stability, solubility and biocompatibility, and can maintain integrity in blood circulation and effectively break when releasing drugs in tumor cells [19]. The selection of drugs requires high cytotoxic activity, low molecular weight and good chemical reactivity, and can form stable conjugates with linkers [20]. The selection of conjugation methods requires controlling the drug-to-antibody ratio (DAR), avoiding too high or too low DAR affecting the pharmacokinetics, safety and efficacy of ADCs [21]. ADCs are novel biopharmaceuticals that use antibody-specific targeting of tumor cells and link drug carriers to antibodies through linkers [22]. ADCs can achieve efficient tumor treatment while reducing toxic side effects on normal tissues. ADCs consist of three components: antibody, linker and drug carrier. Antibody refers to a monoclonal antibody that can recognize and bind to a specific antigen on tumor cells, responsible for delivering ADCs to tumor cells; linker refers to a chemical bond that connects antibody and drug carrier, responsible for ensuring the stability of ADCs in blood circulation and releasing drug carrier inside tumor cells; drug carrier refers to a small molecule compound with cytotoxic activity that is connected to antibody, responsible for killing tumor cells [23, 24].

Currently marketed or in clinical trials ADCs mainly have three generations, distinguished by their linkers, drugs and conjugation methods. The first generation ADCs use acid-sensitive or non-cleavable linkers, combined with mouse-derived or human-mouse chimeric antibodies. The drugs are natural product derivatives such as calicheamicin or maytansine. The conjugation method is random conjugation [25]. The second generation ADCs use tissue protease cleavable or non-cleavable linkers, combined with humanized or fully human antibodies. The drugs are synthetic small molecules such as microtubule stabilizers or topoisomerase I inhibitors. The conjugation method is random conjugation or partial site-specific conjugation [26]. The third generation ADCs use non-cleavable or dual-functional linkers, combined with fully human antibodies. The drugs are novel small molecules such as DNA cross-linkers or topoisomerase I inhibitors. The conjugation method is completely site-specific conjugation [27].

4. Application of Antibody-Drug Conjugates in Childhood Leukemia

4.1. Acute Lymphoblastic Leukemia

Childhood lymphocytic leukemia is a malignant hematologic disorder caused by abnormal proliferation of lymphocyte precursors, mainly comprising B-cell acute lymphoblastic leukemia (B-ALL) and T-cell acute lymphoblastic leukemia (T-ALL). Although conventional chemotherapy regimens have achieved a cure rate of over 80% for childhood lymphocytic leukemia, some patients still fail to respond or relapse, with extremely poor prognosis.

The application of ADCs in childhood lymphocytic leukemia mainly focuses on B-ALL, because B-ALL cells have some ideal targets, such as CD19, CD22, CD79b, etc [28]. Currently, two ADCs targeting B-ALL have been approved by the US Food and Drug Administration (FDA): Inotuzumab ozogamicin (IO) and Blinatumomab. IO is an ADC targeting CD22, consisting of an anti-CD22 antibody and calicheamicin [29]. Calicheamicin is a potent toxin that can cleave DNA double strands, leading to tumor cell apoptosis [30]. IO was approved by the FDA in 2017 for the treatment of relapsed or refractory B-ALL patients. The initial dose of IO should be adjusted according to the patient's body surface area, treatment response and toxicity reactions. Each cycle is divided into three doses, which are given on day 1, day 8 and day 15 respectively. In the first cycle, the recommended total dose of IO is 1.8 mg/m^2, divided into three doses, which are given on day 1 (0.8 mg/m^2), day 8 (0.5 mg/m^2) and day 15 (0.5 mg/m^2) respectively. The duration of the first cycle is 3 weeks, but it can be extended to 4 weeks if the patient achieves complete remission (CR) or complete remission with incomplete hematologic recovery (CRi), and/or to recover from toxicity. In subsequent cycles: (1) For patients who achieve CR or CRi, the recommended total dose of IO per cycle is 1.5 mg/m^2, divided into three doses, which are given on day 1 (0.5 mg/m^2), day 8 (0.5 mg/m^2) and day 15 (0.5 mg/m^2) respectively. The duration of subsequent cycles is 4 weeks each. (2) For patients who do not achieve CR or CRi, the recommended total dose of IO per cycle is 1.8 mg/m^2, divided into three doses, which are given on day 1 (0.8 mg/m^2), day 8 (0.5 mg/m^2) and day 15 (0.5 mg/m^2) respectively. The duration of subsequent cycles is 4 weeks each. Patients who do not achieve CR/CRi within 3 cycles should discontinue IO treatment. In a randomized controlled trial, IO significantly improved the complete remission rate (81% vs 29%), median overall survival (7.7 months vs 6.2 months) and hematopoietic stem cell transplantation rate (48% vs 22%) of relapsed or refractory B-ALL patients compared with standard

chemotherapy [31].

Currently, the FDA has not approved IO for the treatment of childhood acute lymphoblastic leukemia, so there is no clear dose selection to guide pediatric use. Erica Brivio et al reported the safety and efficacy of IO in relapsed or refractory CD22-positive childhood acute lymphoblastic leukemia patients with a total effective rate of 80% (20/25 patients), of which 84% of responders achieved MRD-negative complete remission and a 12-month overall survival rate of 40%. The study determined the recommended second-cycle dose as 1.8 mg/m^2, which is the same as adults [32]. In addition, several studies reported IO initial cycle dose selection in children with B-ALL: (1) total dose of 1.2 mg/m^2 (0.6-0.3-0.3 mg/m^2) [33]; (2) total dose of 1.8 mg/m^2 (0.8-0.5-0.5 mg/m^2) [34]; (3) total dose of 1.4 mg/m^2 (0.6-0.4-0.4 mg/m^2) [35]; all children receiving IO treatment achieved complete remission.

Blinatumomab is a bispecific antibody (BsAb), consisting of two different antibody fragments that can recognize and bind to CD19 and CD3 respectively [36]. CD19 is an antigen on B-ALL cells and CD3 is an antigen on T cells. By connecting them together, blinatumomab can make T cells contact with B-ALL cells and activate T cell killing function, thereby eliminating B-ALL cells [37]. Blinatumomab is not strictly an ADC because it does not have a drug carrier but uses T cell killing function instead. But it can still be considered as an antibody-drug conjugate because it combines two different antibody fragments to form a biopharmaceutical with dual functions. Blinatumomab was approved by the FDA in 2014 for the treatment of relapsed or refractory B-ALL patients. Blinatumomab consists of four weeks of continuous intravenous infusion and two weeks of rest interval per cycle. For children weighing < 45 kg, the dose for the first cycle is: day 1-7:5 μg/m^2/day (maximum dose: 9 μg/day); day 8-28: 15 μg/m^2/day (maximum dose: 28 μg/day). The subsequent cycle dose is: day 1-28: 15 μg/m^2/day (maximum dose: 28 μg/day). Studies have shown that Blinatumomab compared with standard chemotherapy significantly improved the complete remission rate (44% vs 25%), median overall survival (7.7 months vs 4.0 months) and hematopoietic stem cell transplantation rate (40% vs12%) of relapsed or refractory B-ALL patients [38].

No ADCs targeting T-ALL have been approved for marketing, and some drugs are undergoing clinical trials or preclinical research, such as ADCs targeting CD3, CD5, CD7, CD37 and other antigens. IMGN632: an ADC targeting CD123 (leukemia stem cell-associated antigen), consisting of an anti-CD123 antibody and DM4 (a microtubule stabilizer) [39]. DM4 is a potent toxin that can cleave DNA double strands leading to tumor cell apoptosis. IMGN632 received FDA breakthrough therapy drug qualification in2019 for the treatment of relapsed or refractory B-ALL and BPDCN (a rare leukemia). A phase Ib/II clinical trial is currently underway to evaluate the safety and efficacy of IMGN632 in relapsed or refractory B-ALL, T-ALL and AML. ADCT -301: an ADC targeting CD25 (interleukin-2 receptor α chain), consisting of an anti -CD25 antibody and PBD (pyrolo[2,1 -c][1,4]benzodiazepine) [40]. PBD is a potent toxin that can cleave DNA double strands leading to tumor cell apoptosis. ADCT-301 is currently undergoing a phase I clinical trial to evaluate its safety and efficacy in relapsed or refractory B-ALL, T-ALL and NHL. AFM13: an ADC targeting CD30 (lymphocyte activation marker), consisting of two different antibody fragments that can recognize and bind to CD30 and CD16A respectively [41]. CD16A is an antigen on natural killer cells (NK cells), responsible for mediating NK cell anti-tumor activity. By connecting them together, AFM13 can make NK cells contact with T-ALL cells and activate NK cell killing function, thereby eliminating T-ALL cells. A phase I/II clinical trial is currently underway to evaluate the safety and efficacy of AFM13 in relapsed or refractory T-ALL.

In addition, there are some ADCs undergoing clinical trials in childhood lymphocytic leukemia, such as loncastuximab tesirine targeting CD19, polatuzumab vedotin targeting CD79b, mosunetuzumab targeting CD20, etc These ADCs are expected to bring more treatment options and better prognosis for childhood lymphocytic leukemia patients [42 -44].

4.2. Acute Myeloid Leukemia

ADCs are biopharmaceuticals with great potential and prospects, and have achieved significant clinical effects in childhood B-ALL, providing a new treatment strategy for these patients. However, in childhood T-ALL, the application of ADCs is still in the exploratory stage, and more research and trials are needed to discover more effective and safer ADCs. Currently, one ADC for childhood AML has been approved by the FDA: Gemtuzumab ozogamicin (GO). GO is an anti-CD33 antibody conjugated with calicheamicin, CD33 is a widely expressed antigen on AML cells. GO can bind to CD33 and be internalized, releasing chemotherapy drugs, thereby inducing apoptosis of AML cells [45]. GO was initially approved by the FDA in 2000, but was withdrawn in 2010 due to lack of efficacy and severe hepatic veno-occlusive disease. However, based on new clinical trial data, the FDA re-approved GO in 2017 as part of first-line treatment for childhood AML. The most common dose of GO in childhood AML treatment is 3 mg/m^2/dose, which can be used in combination with standard chemotherapy or alone. Compared with chemotherapy alone, adding GO can improve event-free survival (EFS) and reduce relapse risk. However, adding GO did not significantly improve overall survival (OS), possibly due to its increased treatment-related mortality [46]. In addition, another dose of GO used in childhood AML is 6 mg/m^2/dose, which is only seen in relapsed or refractory AML patients and can only be used alone. Compared with 3 mg/m^2/dose, 6 mg/m^2/dose can improve remission rate and progression-free survival (PFS), but also increase toxicity reactions, especially liver toxicity and infection [47]. In summary, the dose selection of GO in childhood AML needs to consider the patient's genotype, treatment regimen, treatment response and toxicity reactions. There is no uniform standard at present and it needs to be adjusted according to individual circumstances. Generally speaking, it is recommended to use 3 mg/m^2/dose as the initial dose and adjust it appropriately according to the actual situation.

4.3. Adverse Reactions in Antibody-Drug Conjugates Therapy

Although ADCs have high-efficiency tumor treatment effects, they may also induce some adverse reactions, including hematological, liver, neurological and ocular toxicity, which may be due to non-specific effects caused by premature release of drug carriers in blood circulation. The incidence and severity of adverse reactions may be related to the drug carriers, dose, administration regimen and tumor type [48]. Common ADC adverse reactions include: (1) Anemia: a decrease in red blood cells or hemoglobin in the blood, leading to a decrease in oxygen delivery capacity, clinically manifested as fatigue, dizziness, palpitations, etc Anemia may be due to drug carrier-induced inhibition or hemolysis of bone marrow; its management methods include monitoring blood routine indicators, transfusing red blood cell suspension, using erythropoietin, etc [49]. (2) Neutropenia: a decrease in neutrophils can lead to an increased risk of infection, clinically manifested as fever, chills, cough, etc Neutropenia may be due to drug carrier-induced inhibition or immune-mediated lysis of bone marrow; its management methods include monitoring blood routine indicators, using granulocyte colony-stimulating factor, preventing and treating infection, etc [50]. (3) Thrombocytopenia: refers to a decrease in platelets in the blood, leading to an increased risk of bleeding, clinically manifested as skin purpura, gingival bleeding, epistaxis, etc Thrombocytopenia may be due to drug carrier-induced inhibition or immune-mediated lysis of bone marrow; its management methods include monitoring blood routine indicators, transfusing platelet suspension, using thrombopoietin, etc [51]. (4) Hepatotoxicity: drug carrier-induced liver damage, leading to liver dysfunction, clinically manifested as elevated transaminases, jaundice, ascites, etc Hepatotoxicity may be due to direct damage or immune-mediated damage of drug carriers to hepatocytes or bile secretion system; its management methods include monitoring liver function indicators, adjusting dose or discontinuing ADCs, using hepatoprotective drugs or immunosuppressants, etc [52]. (5) Neurotoxicity: drug carrier-induced damage to the nervous system, leading to neurological dysfunction, clinically manifested as peripheral neuropathy, meningitis, epilepsy, etc Neurotoxicity may be due to direct damage or immune-mediated damage of drug carriers to nerve cells or myelin; its management methods include monitoring neurological function indicators, adjusting dose or discontinuing ADCs, using neurotrophic drugs or immunosuppressants, etc [53]. (6) Ocular toxicity: drug carrier-induced damage to the eye, leading to vision loss, keratitis, retinal lesions, etc Ocular toxicity may be due to direct damage or immune-mediated damage of drug carriers to eye tissues; its management methods include monitoring visual acuity and fundus conditions, adjusting dose or discontinuing ADCs, using artificial tears or antibiotic eye drops, etc [54]. (7) Skin toxicity: refers to drug carrier-induced damage to the skin, leading to skin inflammation, erythema, blisters, etc Skin toxicity may be due to direct damage or immune-mediated damage of drug carriers to skin cells or basement membrane; its management methods include monitoring skin conditions, adjusting dose or discontinuing ADCs, using antihistamines or corticosteroids, etc [55].

ADCs have shown promising results in the treatment of childhood leukemia, especially for relapsed or refractory patients. However, ADCs also carry significant adverse reactions, which may limit their clinical application. The reported adverse reactions of ADCs in the treatment of childhood leukemia include: infusion-related reactions, thrombocytopenia, neutropenia, VOD, capillary leak syndrome (CLS), etc [34, 56-58]. Infusion-related reactions are generally acute reactions that occur during or shortly after administration of ADCs, such as fever, chills, nausea, vomiting, hypotension and dyspnea. They are usually mild to moderate and can be managed by prophylactic medication and supportive treatment. Hematological toxicity is the most common and dose-limiting toxicity of ADCs in the treatment of childhood leukemia, which can lead to severe neutropenia, thrombocytopenia and anemia. These adverse reactions can increase the risk of infection, bleeding and transfusion dependence. Hematological toxicity may require dose reduction, delay or discontinuation of ADCs, or even prophylactic or therapeutic use of growth factors and antibiotics. VOD is a life-threatening complication of ADC treatment, which can lead to portal hypertension, ascites, hepatomegaly and renal failure, and can be treated with defibrotide. Capillary leak syndrome (CLS) can lead to hypotension, edema, hypoalbuminemia and organ failure. Its onset may be related to antibody-induced cytokine release syndrome or cytotoxic drug-induced vascular damage. Although ADCs are powerful weapons for the treatment of childhood leukemia, they also bring high-risk toxicity that requires careful monitoring and management. Future research should focus on optimizing the design and administration of ADCs to improve their efficacy and safety.

GO dose selection in childhood AML is related to its efficacy and toxicity. Different clinical trials have used different dose regimens, but there is no uniform standard at present. Generally speaking, the higher the dose, the better the efficacy, but the greater the toxicity. Therefore, dose adjustment is needed according to the individual situation and treatment response of the patient. GO dose is significantly correlated with its toxicity reactions. Following the increases of dose, the probability of severe adverse reactions also increases. The most common adverse reactions are liver toxicity, hematological toxicity, infection and gastrointestinal reactions. Among them, liver toxicity is the most serious and difficult to prevent and treat adverse reaction, which may lead to liver failure, veno-occlusive syndrome or intrahepatic venous thrombosis. Studies have shown that GO dose is also related to its efficacy in childhood AML. As the dose increases, the probability of achieving complete remission (CR) or partial remission (PR) also increases. However, too high a dose may also lead to treatment failure or death. Therefore, a balance point needs to be found between dose and efficacy. The reported GO administration doses are mainly

three; 3 mg/m^2, 6mg/m^2 and 9 mg/m^2. Studies have shown that 9 mg/m^2 dose has the highest CR/PR rate (75%), but also has the highest rate of severe adverse reactions (100%) and treatment failure or death (50%). Therefore, this dose may not be suitable for childhood AML patients. 3 mg/m^2 dose has a CR/PR rate of about 50%, but its rate of severe adverse reactions (56.3%) and treatment failure or death (18.8) are also lower. Therefore, 3 mg/m^2 may be a safer and more effective choice. In addition, 6 mg/m^2 dose may be suitable for some patients who are ineffective or have a higher risk of relapse with conventional doses. In total, 16 studies met the inclusion criteria for the systematic review and their characteristics are displayed in Table 1. Among them, 8 studies referred to treatment of ALL with IO and 8 to treatment of AML with GO. All the studies referred to clinical outcomes. In 7 of the eligible studies a combination of ADR was assessed, 13 referred to adjunctive medications. Based on 16 included studies in this review, the vast majority of patients achieved hematologic remission with ADC therapy. The adverse reactions caused by ADC recorded in all studies include: neutropenia with fever, gastrointestinal symptoms, VOD, cytokine syndrome, infection, sepsis, gastrointestinal symptoms, hyperglycemia, hyperphosphatemia, anemia, thrombocytopenia, tumor lysis syndrome, liver function damage, altered mental state and abdominal swelling. Further studies are required to determine the optimal dose, duration, and the best formulation of ADC to prevent and/or manage chemotherapy-induced complications.

5. Prospect

ADCs are revolutionary anti-tumor bioweapons, but they also face challenges and difficulties: (1) Heterogeneity of ADCs: The ratio of drug to antibody may vary in the same batch of ADC products due to different coupling methods and conditions, which may affect their stability, pharmacokinetics and efficacy. (2) Bystander effect of ADCs: Some ADC drugs release small molecule drugs that can penetrate the cell membrane and affect the adjacent non-target cells, causing off-target toxicity. This effect can be beneficial for tumor cells with low or no expression of target antigens, but harmful for normal tissue cells [59]. (3) Protein aggregation of ADCs: ADCs are large molecular complexes that are prone to protein aggregation, which can reduce their solubility, stability and activity, increase their immunogenicity and toxicity, and even cause infusion reactions [60]. (4) Endocytosis efficiency of ADCs: ADCs need to be internalized by tumor cells to release drugs, so endocytosis efficiency is an important factor affecting ADC efficacy. However, not all target antigens have high endocytosis rates, some may even circulate or recycle on the cell surface, thus reducing the endocytosis efficiency of ADCs [61]. (5) Therapeutic window of ADCs: ADCs have both high specificity of antibody drugs and high toxicity of small molecule drugs, so a suitable therapeutic window needs to be found between effective dose and safe dose. The therapeutic window of ADCs is influenced by many factors, such as the expression level of target antigen, the ratio of drug to antibody, the stability and activity of linker and drug [62]. (6) Drug resistance of ADCs: ADC drugs mainly kill tumor cells by interfering with their DNA or microtubule function, so they may encounter similar drug resistance mechanisms as traditional chemotherapy drugs, such as drug efflux, DNA repair, microtubule mutation, etc In addition, there may also be specific drug resistance mechanisms such as target antigen down-regulation or mutation, linker hydrolysis or metabolism [63].

To address these challenges, some innovative and optimized measures are being carried out, mainly including the following aspects: First, optimize the structure and function of antibodies. Through engineering means, the properties of antibodies such as affinity, stability, endocytosis and drug loading can be modified to improve the efficiency and safety of ADCs. For example, bispecific antibodies or bivalent antibodies can be used to target two different antigens simultaneously to enhance the selectivity and killing power of ADCs [64]. Second, improve the design and synthesis of linkers. Through chemical or biological techniques, linkers with different types, locations and numbers can be prepared to achieve precise control of drug release. For example, enzymatic or photosensitive reactions can be used to cleave linkers under specific conditions to reduce toxicity to normal tissues [65]. Third, explore new drug carriers and combination therapies. Through synthesis or screening, new drug carriers with novel structures and mechanisms can be discovered to expand the therapeutic range and effect of ADCs. For example, gene therapy techniques such as RNA interference and CRISPR-Cas9 can be used as drug carriers for ADCs to achieve more precise and lasting therapeutic effects. In addition, ADCs can also be combined with other types of drugs or treatments such as radioisotopes, immune checkpoint inhibitors, targeted small molecule drugs, etc, to enhance the synergistic effect and overcome drug resistance [10].

ADCs are biopharmaceuticals with great potential and promise, but they also face some challenges and difficulties. I believe that with the continuous advancement of science and technology and clinical trials, more and better ADCs will be developed in the future, bringing more hope and benefit to patients. To conclude, ADCs are biopharmaceuticals with great potential and promise, but they also face some challenges and difficulties. I believe that with the continuous advancement of science and technology and clinical trials, more and better ADCs will be developed in the future, bringing more hope and benefit to patients.

6. Conclusion

ADC is a targeted therapy strategy that uses specific antibodies to bind to cytotoxic drugs, and have shown some efficacy and safety in pediatric hematologic malignancies. Among them, the most commonly used ADC is gemtuzumab ozogamicin (GO), which targets CD33 and has been approved for the treatment of relapsed or refractory pediatric acute myeloid leukemia (AML). The dose and adverse reactions of GO vary in different clinical trials, but generally, the dose of

GO is between 3 and 9 mg/m^2, given once a week or every two weeks, either alone or in combination with chemotherapy. The most common adverse reaction of GO is hepatotoxicity, including hyperbilirubinemia, elevated transaminases, and sinusoidal obstruction syndrome (SOS). Other adverse reactions include bone marrow suppression, infection, bleeding, nausea, vomiting, etc. The hepatotoxicity of GO is positively correlated with the dose, so it is necessary to closely monitor liver function and adjust the dose or stop the drug when necessary. The hepatotoxicity of GO may also increase the transplant-related mortality after allogeneic hematopoietic stem cell transplantation (HSCT), so it is necessary to carefully select the timing and conditioning regimen of transplantation. In addition to GO, there are some other ADCs that are undergoing clinical trials in pediatric hematologic malignancies, such as inotuzumab ozogamicin (InO) targeting CD22, blinatumomab-kanamycin (Blino) targeting CD19, and brentuximab vedotin (Brentu) targeting CD30. The dose and adverse reactions of these ADCs need to be further evaluated, but the current data show that they have potential therapeutic value for some refractory or relapsed pediatric hematologic malignancies. In summary, ADCs are a promising treatment modality for pediatric hematologic malignancies, but they still need to optimize the dosing regimen and safety evaluation, and explore the combination strategies with other treatment methods.

Recommendation

IO is one of ADCs targeting B-ALL. The FDA has not approved IO for the treatment of childhood acute lymphoblastic leukemia, so there is no clear dose selection to guide pediatric use.

GO is the recommend ADC for childhood AML. It is recommended to use 3 mg/m^2/dose as the initial dose and adjust it appropriately according to the actual situation.

Abbreviations

RCT, randomised controlled trial; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CR, complete relief; MRD, measurable residual disease; EML, extramedullary leukemia; APL, acute promyelocytic leukemia; IO, inotuzumab ozogamicin; GO, gemtuzumab ozogamicin; ATRA, all-trans retinoic acid; ATO, arsenic trioxide; EFS, event free survival.

Key points: ADCs are associated with unique adverse reactions that may differ from conventional chemotherapy, such as infusion-related reactions, hepatotoxicity, ocular toxicity, and peripheral neuropathy. In this manuscript, we review the current status and challenges of ADCs in the treatment of pediatric AML and ALL. We summarize the clinical trials and outcomes of ADCs in these diseases, as well as the mechanisms and management of their adverse reactions. We also discussed the future directions and perspectives of ADCs in pediatric leukemia.

Running heading: Antibody-drug conjugate in pediatric leukemia.

Author Contribution

Z. L. and X. C. F. searched the databases, wrote the manuscript, and prepared the figures, M. Z. and S. Y. H. defned the manuscript's subject and L. Y. F. edited the manuscript.

Data Availability

No data associated in the manuscript.

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Conflicts of Interest

The authors declare no competing interests.

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