Research Article ISSN 2689-1069

Clinical Reviews & Cases

Integrating Hematopoietic Stem Cell Transplantation (HSCT) and Targeted Antibody-Drug Conjugates (ADCs) in Leukemia Treatment: Current Landscape, Translational Advances, and Emerging Therapeutic Horizons

Malika Salhi*

Hématologie, Oncogenèse, Biothérapies et Biotechnologies, Université Paris Cité, Paris, France.

***Correspondence:**
Malika Salhi, Hématologie, Oncogenèse, Biothérapies et Biotechnologies, Université Paris Cité, Paris, France.

Received: 24 Nov 2024; **Accepted:** 28 Dec 2024; **Published:** 04 Jan 2025

Citation: Salhi M. Integrating Hematopoietic Stem Cell Transplantation (HSCT) and Targeted Antibody-Drug Conjugates (ADCs) in Leukemia Treatment: Current Landscape, Translational Advances, and Emerging Therapeutic Horizons. Clin Rev Cases. 2025; 7(1): 1-10.

ABSTRACT

In recent years, the landscape in the treatment of haematological malignancies, including leukaemia, has rapidly evolved. Hematopoietic stem cell transplantation (HSCT) retains its prominent role in the treatment of leukaemia, but its application continues to be associated with high mortality and graft-versus-host disease (GVHD). Novel therapies like Antibody-drug conjugates (ADCs) have shown potent anti-leukaemia activity and survival benefits in patients, demonstrating their potential as effective agents. Despite these advancements, challenges such as toxicity and acquired resistance, still need to be addressed. This review describes the current state and future directions of HSCT and ADCs in leukaemia, emphasizing the potential of these innovative approaches to transform treatment paradigms and improve patient outcomes. We will explore the current clinical practices and ongoing studies on combining different therapies, crucial and evolving research areas aimed at maximizing efficacy while minimizing toxicity in the patients.

Keywords

Hematopoietic Stem Cell Transplantation (HSCT), Antibody-Drug Conjugates (ADCs), Leukemia Treatment, Translational Advances in Oncology, Emerging Therapeutic Horizons.

Abbreviations

HSCT: hematopoietic stem cell transplantation, GVHD: graft-versus-host disease, ADCs: antibody-drug conjugates, NK: natural killer, AML: myeloid leukaemia, CML: chronic myeloid leukaemia, ALL: acute lymphocytic leukaemia, CLL: Chronic lymphocytic leukaemia, LBCL: large B-cell lymphoma, OS: overall survival, LFS: leukaemia-free survival, DFS: disease-free survival, RFS: relapse-free survival, CR: complete remission, HLA: human leukocyte antigen, haplo-SCT: Haploidentical stem cell transplantation, TRM: transplant-related morbidity and mortality, MSD: HLA-matched sibling donor, CR1: first complete remission, NRM: non-relapse mortality, GVL: graft-versus-leukaemia, MRD: minimal residual disease, DLI: donor lymphocyte infusion, mAbs: monoclonal antibody, FDA: Food and Drug Agency, GO: Gemtuzumab ozogamicin, AML: acute myeloid leukaemia, DLBCL: diffuse large B-cell lymphoma, HCL: hairy cell leukaemia, HL: Hodgkin lymphoma, MMAE: monomethyl Auristatin E, MMAF: monomethylauristatin F, ELN: The European Leukaemia Net, NCCN: National Comprehensive Cancer Network, TKI: Tyrosine Kinase Inhibitor.

Introduction

Haematological malignancies are a heterogeneous group of cancers originating from uncontrolled growth of hematopoietic stem cells (HSCs), which compromise the differentiation of red blood cells, white blood cells, and platelets [1]. The risk factors generally associated with haematological malignancies are genetic and epigenetic alterations, environmental exposure to toxins, such as ionizing radiation, and chronic inflammation [2-4]. Haematological malignancies are among the ten leading cancer types diagnosed in both men and women and are categorized into leukaemia, lymphoma, and multiple myeloma [5,6]. Leukaemia originates in the bone marrow and is characterized by an abnormal proliferation of white blood cells known as blasts or leukaemia cells [7]. Lymphoma is caused by alterations of T cells, B cells, or natural

killer (NK) cells and is categorized into Hodgkin lymphoma and non-Hodgkin lymphoma. Multiple myeloma affects plasma cells in the bone marrow [7,8]. Leukaemia is the most common childhood cancer and accounts for 28% of cancer cases in 2024 among children [5]. The accumulation and proliferation of malignant cells in the bone marrow and other tissues, such as the liver, lymph nodes, and spleen lead to damage to their function [9]. Leukaemia is classified into acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), acute lymphocytic leukaemia (ALL), and chronic lymphocytic leukaemia (CLL). This classification depends on the type of cells (lymphoid or myeloid cells) affected and the rapidity of tumour cell proliferation (acute or chronic) [7,8].

AML is one of the most common types of leukaemia and is characterized by an uncontrolled growth of immature blast cells, which leads to the formation of aberrant red blood cells and bone marrow failure [10]. The chronic leukaemia subtypes occur more often in adults and the disease development is slower and less lethal [11].

ALL has a higher prevalence in children and is caused by genetic alterations that affect the development and proliferation of lymphoid cells. CLL is instead more prevalent in adults in Western countries and characterized by the proliferation and accumulation of monoclonal B lymphocytes in the peripheral blood, bone marrow, and lymphatic system [8,11]. Depending on the leukaemia subtype and the respective risk group, patients are treated with appropriate therapies. The main goal of leukaemia treatments is to destroy the malignant cells and re-establish the normal hematopoietic function of the bone marrow [9,12]. The treatment for leukaemia consists of hematopoietic stem cell transplantation (HSCT), chemotherapies, and targeted drug therapy. Targeted therapies hold promise to overcome current challenges with standard therapy and include immunotherapies, such as Chimeric antigen receptor T-cell (CAR-T) therapies, Tyrosine kinase inhibitors (TKI), and Antibody-drug conjugates (ADCs) [11,12]. HSCT involves the administration of healthy HSCs to patients with dysfunctional bone marrow. This therapy plays a crucial role in the treatment of patients with refractory, recurrent leukaemia and for children with high-risk or relapsed ALL and AML [9,13,14]. Autologous HSCT (auto-HSCT) has been the standard therapy for aggressive lymphomas and myeloma, while allogeneic HSCT (allo-HCST) has been the pillar of AML treatment [15]. Although auto-HSCT and allo-HSCT have more side effects than chemotherapy and immunotherapy, allo-HSCT is still a crucial treatment option for poor and very-poor-risk patients with AML and children with high-risk or relapsed ALL [13,16].

Chemotherapy is commonly used for various types of leukaemia and is associated with decent complete remission and overall survival. However, chemotherapeutic drugs are associated with severe toxicity and none of them are first-line treatments for elderly patients with AML and CLL [12]. TKI used alone or in combination with chemotherapies, has significantly improved patient outcomes but requires careful management due to potential inadequate responses or side effects [11,17,18]. New approaches also combine chemotherapeutic drugs with immunotherapies. However, patients respond differently to chemotherapy and immune escape limits the efficacy of the treatment [9]. CAR-T therapy shows promising results in treating relapsed/refractory large B-cell lymphoma (LBCL) and B-cell ALL. Still, it faces several challenges, like severe toxicities, recurrent disease, and high costs [19–22]. Another promising class of therapy are the ADCs, which are the focus of this review. ADCs are antibody-based drugs that have been extensively researched in recent years, as they selectively target cancer cells and can efficiently eliminate them without harming non-malignant tissue [23]. Since the approval of the first ADCs by the Food and Drug Administration (FDA) in 2000, several ADCs have been released on the market and showed promising results in the treatment of cancers, including leukaemia [23,24]. ADCs have the potential to revolutionize the development of targeted therapies and will likely replace conventional therapies in the future. In this review, we will discuss the mechanism of action and recent advancements of ADCs. We will also focus on exploring the efficacy of ADCs and other targeted therapies with HSCT, describing the evolution of HSCT in recent years.

Methodology

For this systematic review, literature reviews, meta-analyses, and systematic reviews published between January 1, 2014 and 22 September 2024 were searched on PubMed and Google Scholar. Key words used to select the reviews were: hematological malignancies, leukemia, acute myeloid leukaemia, in combination with stem cell transplantation, allo-HCT, auto-HCT, targeted therapies, and antibody-drug conjugates. Non-English-language articles and those not specifically focusing on leukaemia were excluded. Studies that assessed overall survival (OS), leukaemia-free survival (LFS), disease-free survival (DFS), relapse-free survival (RFS), and complete remission (CR) in adults and pediatric patients with leukaemia were included.

Hematopoietic Stem Cell Transplantation (HSCT)

Principles and types of HSCT, indications, and considerations in acute myeloid Leukemia (AML)

The types of HSTC are classified based on the source of the cells and the relationship between the donor and the recipient. In the past, stem cells were harvested from donor bone marrow, but now with the introduction of granulocyte colony-stimulating- factor, they are mostly obtained from peripheral blood [25,26]. Harvesting the stem cells from the peripheral blood increases the risk of graft-versus-host disease (GVHD), but it provides faster recovery of the immune system and white blood cells in the recipient, and a lower incidence of graft failure [25,27].

Stem cells can also be harvested from the umbilical cord blood, but in a reduced amount in comparison to the bone marrow and the peripheral blood. This might slow the immune reconstitution process [27]. HSCT can be autologous (auto-HSCT) if the stem cells are harvested from a recipient or allogeneic (allo-HSCT) if the cells are collected from a donor or umbilical cord blood units [25,27]. In allo-HSCT, a suitable related or unrelated donor with acceptable human leukocyte antigen (HLA) compatibility must be identified.

If a donor cannot be found, a partially matched family member (a "haploidentical" donor) or banked umbilical cord blood units are used [25]. Haploidentical stem cell transplantation (haplo-SCT) is shown to decrease relapse and improve survival in specific types of AML patients. The high success of haplo-SCT is linked to an improvement in transplantation techniques, such as conditioning regimen modification, GVHD prophylaxis, and donor selection. However, relapse and infections are the causes of death and limit the success of the therapy [28]. Allo-HSCT is indicated for AML and ALL, with patients reporting better OS, RFS and DFS than auto-HSCT treatment [25,29]. However, allo-HSCT can cause transplant-related morbidity and mortality (TRM), whose risk and severity are increased when an HLA-matched sibling donor (MSD) is absent and an alternative donor graft is used [16]. Auto-HSCT has no limitation of cell donor source and is associated with lower TRM but might cause a higher relapse rate. The prognosis of patients is poor with more than 50% of patients with AML who relapse after transplantation [29].

Analysis of Clinical Trial Outcomes

Allo-HSCT improved LFS and OS for patients with AML, especially those in first complete remission (CR1), with unfavourable cytogenetics aged 41-60. In these patients, allo-HSCT decreased the incidence of non-relapse mortality (NRM) [30]. AML patients in CR1 might be considered also eligible for auto-HSCT if they do not present unfavourable cytogenetics [31]. Auto-HSCT is associated with a higher rate of relapse than allo-HSCT due to the absence of a graft-versus-leukaemia (GVL) effect by allogeneic cells. However, data showed comparable LFS between auto-HSCT and allo-HSCT in AML patients in CR1 with normal or intermediate cytogenetics [32,33]. Although allo-HSCT should be preferred in AML patients during CR1, only 30% of patients find HLA-MSDs. When matched donors are unavailable, haplo-SCT is a valid alternative in AML patients, as recent studies showed no statistically significant differences between MSD-HSCT and haplo-SCT [28,34]. Allo-HSCT is highly recommended for relapsed/refractory AML and ALL, especially in adult and paediatric patients with high-risk T-ALL in CR1. In these patients, allo-HSCT offers long-term remission [29,35,36]. Allo-HSCT provides better survival outcomes also in patients with relapsed/refractory B-cell ALL, with a prolonged 5-year survival probability of 24.4-28.4% [37]. AML patients with refractory disease are 10% to 40% of all diagnosed AML. Only 10% of these patients achieve CR after chemotherapy and their OS tends to increase by 20% to 25% after transplantation. The treatment of these patients remains challenging and allo-HSCT is still the therapy that guarantees longer survival [36]. The timing of allo-HSCT is crucial for these patients who should undergo transplantation as soon as possible. Data showed better outcomes when HSCT was performed in the first complete remission (CR1) compared to later stages [39].

Advancements in HSCT Therapy and Future Directions to Address Remaining Challenges

Relapse remains the major problem limiting the success of transplantation [28,40]. It occurs in 40-50% of AML patients after undergoing transplantation. For these patients, the prognosis is poor with a 3-year survival rate [41].

Recent advancements in HSCT have improved outcomes for leukaemia patients undergoing transplantation. The introduction of post-transplant cyclophosphamide for GVHD prophylaxis has contributed to increased donor availability and reduced risk of GVHD [40]. Improvements have also been made in minimal residual disease (MRD) monitoring strategies, in identifying predictions of transplant risks, and in understanding the biological characterisation of AML [40].

Table 1: Strategies to improve the use of HSCT and ADCs and subsequent advantages.

HSCT	
Strategies	**Advantages**
Post-transplant cyclophosphamide for GVHD prophylaxis	• Increased donor availability • Reduced risk of GVHD
Monitoring of MRD	• Better predictions of transplant risks • Better biological characterisation of AML
Pre-transplantation of γδ T cells in MRD-positive patients	• Decreased rate of relapse • Improved survival
Haplo-SCT advancements	• Decrease rate of relapse and GVHD • Improved survival
Identification of genomic abnormalities	• Improved prognosis • Better categorization of patients
Use of DLI	• Decrease in the rate of relapse
Use of microtransplantation	• Decrease rate of relapse • Less side effects of HSCT
• ADCs	
Improvement of the linker stability	• Less off-target toxicity
Modification of the cytotoxic drug	• More potent cytotoxic drug • Less off-target toxicity
Development of bispecific antibodies	• Higher rates of remissions • Less post-transplantation disease recurrence
The combinations of ADCs with other treatments (targeted therapies and HSCT)	• Improved survival • Overcoming acquired resistance

Abbreviations: ADCs, antibody-drug conjugates; AML, acute myeloid leukaemia; DLI, donor lymphocyte infusion; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease.

New immunological strategies that reduce the risk of relapse and improve LFS and OS have also been developed [40]. The pre-transplantation of γδ T cells in MRD-positive patients with AML lowers the relapse rate and increases the survival rate without being associated with increased development of GVHD [42]. Advancements in transplant techniques are also leading to better outcomes for patients. Haplo-SCT is now considered a valid alternative to HLA-matched transplantation in AML patients with recent studies showing comparable cumulative incidences of relapse (CIR) and non-relapse mortalities (NRM) [43]. Moreover, haplo-SCT with post-transplant cyclophosphamide (PTCy) leads to lower rates of GVHD [44]. Identifying genomic abnormalities is also a useful technique for improving prognosis and categorizing patients who benefit more from allo-HSCT [41,45]. Additionally, the use of pre-emptive immune strategies, such as donor lymphocyte infusion (DLI), could prevent relapse after allo-SCT in high-risk AML, but careful attention must be paid since DLI might cause severe GVHD and pancytopenia. Novel approaches like microtransplantation aim to expand donor options and reduce the side effects of HSCT. This advanced technology involves consolidative chemotherapy with Cytarabine followed by the infusion of HLA-mismatched peripheral blood stem cells. The concept behind it is that the alloreactive HLA-mismatched cells do not engraft but rather destroy AML clones without inducing GVHD [41]. Micro-transplantation holds promise to be a safe and efficacious strategy for AML treatment. However, further studies are needed to verify its applicability [46,47]. A summary of the strategies under development aiming to improve patient outcomes with the use of HSCT is summarized in Table 1.

Targeted Therapy with Antibody-drug conjugates (ADCs)

Structure and Mechanism of Action

ADCs comprise a monoclonal antibody (mAbs) and a cytotoxic drug covalently attached through a chemical linker. The antibody can recognize and bind to the target antigen which is expressed on cancer cells. Therefore, the target antigen should be exclusively expressed on tumour cells to reduce off-target toxicity. For haematological malignancies, the target antigens of the approved ADCs are normally specific proteins overexpressed in cancer cells, including CD19, CD22, CD33, CD30, BCMA, and CD79b. The cytotoxic drug is the component which destroys cancer cells and commonly is a DNA-damaging agent, a potent tubulin inhibitor, or an immunomodulator.

The chemical linker connects the cytotoxic drug to the antibody and controls the release of the drug in the malignant cells. Their stability in circulation is important to prevent toxicities and premature release of the drug [23]. Therefore, ADCs have the advantage of being both highly specific in targeting cancer cells and potent in killing cancer cells. The ADC recognizes and binds to its target on a cancer cell. Afterwards, the linker is cleaved from the antibody and the cytotoxic drug is endocytosed/internalized inside the cancer cell. The mechanisms of action of the drug are various and determine cell death and apoptosis. It inhibits DNA synthesis causing cancer cell death or stops microtubule formation and function [48].

FDA-approved ADC Cell Products and Their Clinical Applications

ADCs are an important new class of anticancer drugs that offer accurate target binding, good tolerance, and avoidance of off-target toxicity [49].

The FDA approved seven ADCs for the treatment of haematological malignancies (Table 2). These are: Gemtuzumab ozogamicin (GO) (CD33), Brentuximab vedotin (CD30), Inotuzumab ozogamicin (InO) (CD22), Polatuzumab vedotin (CD79B), Belantamab mafodotin (BCMA), Moxetumomab pasudotox (CD22), and Loncastuximab tesirine (CD19) [48,49]. For the specific treatment of leukaemia, the number of approved ADCs is reduced to two, with GO approved for AML and InO for ALL. Moxetumomab pasudotox has also been approved in 2018 for the treatment of patients with relapsed or refractory hairy cell leukaemia (HCL), a rare type of leukaemia [49].

GO is the first ADC that received FDA approval to treat newly diagnosed and relapsed/refractory CD33-positive AML in adults and paediatric patients. GO is a humanized immunoglobulin G4 antibody directed against CD33 and conjugated to the DNA toxin Calicheamicin through a hydrolysable linker. Upon Calicheamicin release, single and double-strand breaks and cellular death are promoted [50]. GO received accelerated approval from the FDA in 2000 after clinical trials showed its positive outcome on CR. In the first phase of the clinical trial, 40 adults with relapsed/refractory AML showed a CR rate of 12.5% after GO administration. In the second phase, 26% of patients in the first relapse who received single-agent GO reached CR. In 2010, Pfizer was forced to withdraw GO from the commercial market after 637 adult patients treated with GO experienced no survival improvement and treatment-related toxicity was increased in comparison to participants receiving standard chemotherapy or chemotherapy with GO [48,49]. Following trials confirmed considerable side effects of GO treatment, such as myelosuppression, hepatotoxicity, infections, infusion reactions, and bleeding, but emphasized that the drug's efficacy outweighs its toxicity [49].

Additional trials showed no significant adverse events and improved OS in elderly patients treated with GO and high CR (83% after 1 course and 87% after 2 courses) in paediatric patients who received GO with standard chemotherapy after HSCT [51,52]. In a subsequent trial, EFS improved when GO was added to standard chemotherapy (53% vs. 46%), whereas OS was not significantly different between the two groups. Considering these results, GO was reintroduced in the market [53]. The other ADC approved for leukaemia, InO, is indicated for the treatment of relapsed or refractory B-cell precursor ALL. InO is a humanized immunoglobulin IgG4 antibody which targets CD22 attached to the antitumor antibiotic Calicheamicin via a cleavable linker. InO is an efficient treatment in adults with B-ALL. In the phase III INOVATE trial, a higher rate of CR was achieved when patients were treated with InO (80%) instead of chemotherapy (29%) [54]. Paediatric patients also benefit from the treatment with InO. In a clinical trial, 71% of a group of 51 paediatric patients

Table 2: FDA-approved ADCs for the treatment of haematological malignancies.

Drugs	Target antigens	Antibody	Linkers	Cytotoxic drugs	Approved indications
Gemtuzumab ozogamicin	CD33	Gemtuzumab	hydrazone	Calicheamicin	AML
Inotuzumab ozogamicin	CD22	Inotuzumab	hydrazone	Calicheamicin	ALL
Moxetumomab pasudotox	CD22	Moxetumomab	mc–VC–PABC	PE38	HCL
Brentuximab vedotin	CD30	Brentuximab	mc–VC–PABC	MMAE	HL, ALCL
Polatuzumab vedotin	CD79B	Polatuzumab	mc–VC–PABC	MMAE	DLBCL
Belantamab mafodotin	BCMA	Belantamab	non-cleavable maleimidocaproyl	MMAF	Multiple myeloma
Loncastuximab tesirine	CD19	Loncastuximab	mc–VC–PABC	PBD SG3199	DLBCL

Abbreviations: ALL: Acute Lymphoblastic Leukaemia; ALCL: Anaplastic Large Cell Lymphoma; AML: Acute Myeloid Leukaemia; DLBCL: Diffuse Large B-cell Lymphoma; HCL: Hairy Cell Leukaemia; HL: Hodgkin Lymphoma; MMAE: Monomethyl Auristatin E; MMAF: Monomethylauristatin F.

receiving InO were negative for MRD, while 67% achieved CR [55]. A subsequent clinical trial recruiting 53 paediatric patients showed 42% of patients with CR and 95.5% of them with negative MRD [56]. These results led to the approval by the FDA of InO for children aged one year and older with relapsed or refractory CD22-positive B-cell precursor ALL. An ongoing study is testing the effects of adding InO to post-induction chemotherapy for people with high-risk B-cell ALL to reduce toxicity and improve outcomes in patients [48].

Challenges of ADCs Applications and Future Directions

ADCs offer the advantage of limited toxicity compared to standard therapy thanks to their target specificity. However, on and off-target tissue damage can occur since the target is also expressed in healthy cells. Additionally, the cytotoxic drug can be prematurely released into the circulation due to linker instability. The common side effects of GO and InO are neutropenia, anaemia, hepatic toxicity, thrombocytopenia, and peripheral neuropathy [57]. Calicheamicin, contained in both GO and InO, is responsible for hepatotoxicity including hyperbilirubinemia, elevated transaminases, and sinusoidal obstructive syndrome (SOS) [58]. Other considerations include determining the necessary level of CD33 expression to achieve a survival benefit, as patients with low CD33 expression may not benefit from GO treatment [48].

The internalization and lysosomal processing of the antigen/ADC complex is often inefficient, leading to the inefficacy of the treatment. To increase internalization and lysosomal targeting bispecific antibodies are now under development. These novel drugs have one binding arm which binds the tumour cell and another binding arm responsible for facilitating internalization and lysosomal delivery of the toxic drug. The use of bispecific antibodies could potentially increase the pool of potential ADC targets that fail to internalize or do it poorly. Recently, enhanced internalization and lysosomal accumulation in HER2-positive tumour cells were shown with the use of a bispecific ADC targeting both HER2 and CD63 [59]. A summary of the strategies under development aiming to improve patient outcomes with the use of ADCs is summarized in Table 1.

Novel ADCs are under study to reduce the toxicity of GO and InO. However, these drugs showed severe side effects, such as nausea, diarrhoea, fatigue, and febrile neutropenia [48]. Vadastuximab talirine, or SGN-CD33A, contains a humanized IgG1 CD33 antibody and carries a highly potent DNA crosslinking pyrrolobenzodiazepine (PBD) dimer [48,60]. However, its development was discontinued due to fatal infections which led to higher rates of deaths. Moreover, concerns were also raised regarding liver toxicity [48,60]. The development of another ADC, SGN-CD123A, was also terminated as it contained the identical PBD dimer and linker molecules of SGN-CD33A that caused excessive toxicities [49,61]. Ongoing studies are testing the efficacy and safety of IMGN632, which contains a cysteine-engineered humanized CD123 IgG1 antibody attached to a DNA mono-alkylating indolinobenzodiazepine pseudodimer (IGN) [48,60]. A 33% CR rate was shown in a preliminary study with adverse events of nausea, diarrhoea, hypotension febrile neutropenia, and peripheral edema [62]. Coltuximab ravtansine, or SAR3419, is a humanized CD19 antibody with a Maytanisoid DM4 payload which shows modest efficacy in patients with B-ALL [48,60].

HSCT and Targeted Therapies in The Treatment of Leukaemia

Current Indications for HSCT and Issues with Targeted Therapy

Despite the availability of more targeted and safer therapies, HSCT remains the pillar of treatment for specific types of leukaemia patients. The European Leukaemia Net (ELN) and the National Comprehensive Cancer Network (NCCN) guidelines recommend the use of allo-HSCT for AML patients with intermediate-risk or unfavourable-risk cytogenetics, particularly those with poor prognostic factor, who relapse or are refractory. In these cases, allo-HCST is indicated after CR1. ALL patients at high risk, such as Philadelphia chromosome-positive (Ph+) ALL, or those MRD-positive after initial therapy should also undergo allo-HSCT after remission. For CML, allo-HSCT should be considered for patients who do not respond to or are intolerant of TKIs [61,63]. These recommendations of the guidelines highlight the pivotal role that HSCT still plays in modern therapy, despite the considerable treatment-related morbidity and mortality. Moreover, they point out the importance of risk stratification and personalized treatment planning in assessing the suitability and timing of stem cell transplantation for leukaemia patients [15,64]. Improvements in transplantation techniques, including innovations in haplo-HSCT and supportive care, have broadened the application of HSCT and demonstrated its continued relevance despite the emergence of new drugs [15]. However, its toxicity demands more effort in improving new drugs that offer high specificity and promising

outcomes for the patients. Moreover, despite the advancements, not all patients are fit for HSCT. Novel therapies, such as CAR-T cells, ADCs, and bispecific antibodies are valid adjunctive to HSCT, as they achieve high rates of remissions and reduce post-transplantation disease recurrence.

The high remission rate and DFS obtained by CAR-T cell therapy suggest that this treatment could be a definitive method for a portion of patients with B-ALL [65]. Nevertheless, more research is needed to determine if therapies like CAR-T cells can fully replace HSCT in the treatment of leukaemia [66-68]. Ongoing research and clinical trials are also studying the efficacy and safety of ADCs in conjunction with other therapies [69,70]. ADCs are a promising alternative to chemotherapy which can reduce toxicity and provide alternatives for patients with poor prognoses and refractory to other treatment options. These treatments are also crucial for those patients who do not tolerate multiple cycles of intensive chemotherapy, such as elderly patients [69,71,72]. However, there remains a significant gap in understanding how to effectively combine ADCs with other treatments to achieve better outcomes and how to overcome acquired resistance. Despite their potent cytotoxicity, tumour cells develop resistance to ADCs through various mechanisms. These are changes in endocytosis mechanisms and vesicular trafficking, altered expression or mutations of antigens, augmented activity of the drug efflux pumps, disparity in pro-apoptotic and anti-apoptotic factors, defects of lysosomal activity, and dysregulation of signalling pathways. The modifications of the cytotoxic drug and the linker, the use of bispecific antibodies, and the combinations of ADCs with other treatments are currently under study to overcome resistance [73,74].

Moreover, despite the reduced toxicity of these treatments in comparison to standard therapy, ADCs still cause toxicity effects that need to be carefully considered [48,69].

Combination Therapies for the Treatment of Leukaemia

Combining targeted therapy with HSCT shows great potential for enhancing patient outcomes in leukaemia treatment [65,75]. Current investigations focus on testing the combination of novel drugs with standard therapies or HSCT in haematological malignancies, including leukaemia [15,69]. The optimal combination of therapies depends on the specific types of leukaemia and the patient´s characteristics.

In AML, the combination of azacitidine (chemotherapeutic drug) and Venetoclax (BCL2 inhibitor), markedly improves outcomes, also when patients have a poor prognosis [76]. An ongoing clinical trial is testing the addition of an ADC, Pivekimab sunirine, targeting CD123, to azacitidine and Venetoclax [77,78]. The combination of fractionated GO with high-dose chemotherapy (cytarabine and mitoxantrone) proved to be a feasible and effective bridge to allo-HSCT for patients with refractory and relapsed AML [79]. EFS is also enhanced when GO is used in combination with Idarubicin, a granulocyte colony-stimulating factor, Fludarabine, and Cytarabine. Future studies need to concentrate on studying the combination of GO with other novel drugs to achieve better outcomes in the patients [80]. GO alone at low dosage is a valid induction therapy as it improves EFS in patients with de novo CD33-positive AML [15]. When administered before HSCT, a lower dose (3 mg/m^2) of GO reduces the risk of SOS [48]. Revised dosing schedules showed also reduced rates of VOD [50].

In CML, TKIs play a pivotal role, showing considerably improved patient survival, while CAR-T therapy has demonstrated high remission rates in relapsed or refractory patients with B-ALL [65,75,81]. Midostaurin (first generation of TKIs) improves post-transplantation survival in patients with AML in combination with standard induction and consolidation chemotherapy [15]. Next-generation TKIs, such as Gilteritinib, are now under investigation for post-transplantation maintenance [82].

The combination of allo-HSCT with CAR-T cells is also an attractive strategy to enhance the prognosis and reduce relapse of patients with high-risk B-ALL. CAR-T therapy could be used as a bridge to allo-HSCT, leveraging its strengths to clear MRD peri-transplantation and treat GVHD [65]. Clinical trials showed that allo-HSCT after CAR-T therapy is effective and safe for patients with refractory and relapse B-ALL and could potentially decrease the incidence of recurrence after CAR-T therapy and enhance the quality of life of patients [45]. Their effects appear to be particularly beneficial for high-risk patients, such as those

Table 3: Selected trials investigating novel therapies in combination with chemotherapies and/or HCST in Leukaemia.

Phase	Diseases Type	Objectives
3	AML	To evaluate the efficacy and safety of azacitidine + Venetoclax, in comparison to Azacitidine + placebo
1b/2	refractory/relapse AML	To evaluate the safety and anti-leukemic activity of Pivekimab sunirine + azacitidine + Venetoclax
1/2	primary refractory or relapsed AML	To evaluate the efficacy and safety of GO + Cytarabine + Mitoxantrone as a bridge to allo-HSCT
3	younger adults with AML	To compare the efficacy of a single dose versus fractionated schedule of GO combined with daunorubicin and Ara-C or Fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin
3	AML	To compare the efficacy of GO+ e first course of intensive induction chemotherapy versus chemotherapy (trials testing DA, ADE, or FLAG-Ida; DA plus G-CSF or GM-CSF; DA or daunorubicin plus clofarabine
1/2	newly diagnosed AML with a FLT3 mutation	To compare the efficacy of crenolanib with that of Midostaurin when administered after induction chemotherapy (daunorubicin and cytarabine), consolidation chemotherapy (cytarabine), and bone marrow transplantation
1-1/2	Refractory/relapse B-ALL	To evaluate the efficacy of CAR-T as a bridge to allo-HSCT

Abbreviations: ALL: Acute Lymphoblastic Leukaemia; AML: Acute Myeloid Leukaemia; DA: Daunorubicin Plus Cytarabine; ADE: Daunorubicin, Cytarabine, and Etoposide. FLAG-Ida: Fludarabine, Cytarabine, G-CSF, and idarubicin; G-CSF: Granulocyte Colony-Stimulating; GO: Gemtuzumab Ozogamicin.

with adverse genes, complex karyotypes, high tumour burden, and high pre-infusion MRD [41,83]. More controversial are the results of studies on AML, where most of the patients died because of the progression of the disease and a low rate of CR was obtained [41]. Therefore, targeted therapies, such as TKIs, CAR-T, and ADCs, can potentially reduce the disease burden before HSCT, making the transplantation process more effective and reducing the risk of relapse. However, the best sequencing and combination of targeted therapies with other treatments or transplantation is still ongoing research that needs to take into account patient individual characteristics, such as genetic mutations. For example, advancements have been made in including molecular and genetic information in the classification of AML to find the most appropriate treatment strategy. For patients in remission who cannot undergo allo-HSCT, maintenance therapy with targeted agents is being explored to prolong remission and improve outcomes [15,69,77].

Conclusion

The development of new targeted drugs has contributed considerably to improving the outcomes of leukaemia patients. ADCs are a promising class of treatments that combine the target specificity of antibodies and the potent killing of chemotherapeutics. ADCs in monotherapy and combination with other treatments showed positive results in leukaemia patients, despite there are multiple areas that still need to be addressed. These include the optimal dosing of ADCs, the acquired resistance, and their mechanisms of toxicity.

For now, targeted therapies are shown to be most effective as adjuncts to transplantation, helping more patients achieve remission and reducing recurrence-related mortality through deeper remissions or maintenance therapy.

While data are still evolving, there is hope that ADCs and other therapies, like CAR-T, TKIs, and bispecific antibodies, will continue to advance, leading to even better outcomes for patients in the future. In this context, HSCT continues to play an important role in the treatment of haematological treatments, including leukaemia. Advancements in transplantations, such as the use of haplo-SCT, paved the way to a more accessible allo-HCT and improved its clinical outcomes.

In summary, future studies should prioritize addressing the challenges associated with targeted therapies. Additionally, further research is essential to determine the optimal leukaemia treatments tailored to specific situations and patient characteristics.

References

1. Keykhaei M, Masinaei M, Mohammadi E, et al. A global, regional, and national survey on burden and Quality of Care Index (QCI) of hematologic malignancies; global burden of disease systematic analysis 1990–2017. Exp Hematol Oncol. 2021; 10: 11.
2. Hu D, Shilatifard A. Epigenetics of hematopoiesis and hematological malignancies. Genes Dev. 2016; 30: 2021-2041.
3. Wade JC. Viral infections in patients with hematological malignancies. Hematology Am Soc Hematol Educ Program. 2006; 368-374.
4. Davis AS, Viera AJ, Mead MD. Leukemia: an overview for primary care. Am Fam Physician. 2014; 89: 731-738.
5. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA: A Cancer Journal for Clinicians. 2024; 74: 12-49.
6. Choi HY, Chang JE. Targeted Therapy for Cancers: From Ongoing Clinical Trials to FDA-Approved Drugs. Int J Mol Sci. 2023; 24: 13618.
7. Choi HS, Kim BS, Yoon S, et al. Leukemic Stem Cells and Hematological Malignancies. International Journal of Molecular Sciences. 2024; 25: 6639.
8. Jiménez C, Garrote-de-Barros A, López-Portugués C, et al. Characterization of Human B Cell Hematological Malignancies Using Protein-Based Approaches. International Journal of Molecular Sciences. 2024; 25: 4644.
9. Zhang Y, Song Y, Ni Q, et al. Systematic review and meta-analysis: transplanted hematopoietic stem cells and killer cells on leukemia. Annals of Palliative Medicine. 2021; 10: 7872883-7877883.
10. Lagunas-Rangel FA, Chávez-Valencia V, Gómez-Guijosa MÁ, et al. Acute Myeloid Leukemia-Genetic Alterations and Their Clinical Prognosis. Int J Hematol Oncol Stem Cell Res. 2017; 11: 328-339.
11. Ito K, Ito K. Leukemia Stem Cells as a Potential Target to Achieve Therapy-Free Remission in Chronic Myeloid Leukemia. Cancers (Basel). 2021; 13: 5822.
12. Wan Z, Sun R, Moharil P, et al. Research advances in nanomedicine, immunotherapy, and combination therapy for leukemia. Journal of Leukocyte Biology. 2021; 109: 425-436.
13. Algeri M, Merli P, Locatelli F, et al. The Role of Allogeneic Hematopoietic Stem Cell Transplantation in Pediatric Leukemia. J Clin Med. 2021; 10: 3790.
14. Sumbly V, Landry I, Sneed C, et al. Leukemic stem cells and advances in hematopoietic stem cell transplantation for acute myeloid leukemia: a narrative review of clinical trials. Stem Cell Investigation. 2022; 9: 10.
15. Bair SM, Brandstadter JD, Ayers EC, et al. Hematopoietic stem cell transplantation for blood cancers in the era of precision medicine and immunotherapy. Cancer. 2020; 126: 1837-1855.
16. Takami A. Hematopoietic stem cell transplantation for acute myeloid leukemia. Int J Hematol. 2018; 107: 513-518.
17. Gill H, Leung AYH, Kwong YL. Molecularly targeted therapy in acute myeloid leukemia. Future Oncol. 2016; 12: 827-838.
18. García-Gutiérrez V, Hernández-Boluda JC. Tyrosine Kinase Inhibitors Available for Chronic Myeloid Leukemia: Efficacy and Safety. Front Oncol. 2019; 9: 603.
19. Huang R, Wang X, Zhang X. Unity brings strength: Combination of CAR-T cell therapy and HSCT. Cancer Letters. 2022; 549: 215721.

20. Moyo TK, Vaidya R. Re-examining the role of hematopoietic stem cell transplantation in relapsed large B-cell lymphoma in the era of chimeric antigen receptor (CAR) T-cell therapy. Front Oncol. 2024; 14: 1397186.
21. Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. Blood Cancer J. 2021; 11: 69.
22. Atrash S, Bano K, Harrison B, et al. Car-T Treatment for Hematological Malignancies. Journal of Investigative Medicine. 2020; 68: 956-964.
23. Fu Z, Li S, Han S, et al. Antibody drug conjugate: the "biological missile" for targeted cancer therapy. Signal Transduct Target Ther. 2022; 7: 93.
24. Hurwitz J, Haggstrom LR, Lim E. Antibody-Drug Conjugates: Ushering in a New Era of Cancer Therapy. Pharmaceutics. 2023; 15: 2017.
25. Bazinet A, Popradi G. A general practitioner's guide to hematopoietic stem-cell transplantation. Curr Oncol. 2019; 26: 187-191.
26. Dessie G, Derbew Molla M, Shibabaw T, et al. Role of Stem-Cell Transplantation in Leukemia Treatment. Stem Cells Cloning. 2020; 13: 67-77.
27. Sugiyanto M, Gosal S, Kosim A, et al. Impact of the source of hematopoietic stem cells on immune reconstitution after transplantation: A systematic review. Eur J Haematol. 2023; 111: 4-14.
28. Chang YJ, Zhao XY, Huang XJ. Haploidentical Stem Cell Transplantation for Acute Myeloid Leukemia: Current Therapies, Challenges and Future Prospective. Front Oncol. 2021; 11: 758512.
29. He P, Liang J, Zhang W, et al. Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia: An Overview of Systematic Reviews. Int J Clin Pract. 2022; 2022: 1828223.
30. Grosicki S, Holowiecki J, Kuliczkowski K, et al. Assessing the efficacy of allogeneic hematopoietic stem cells transplantation (allo-HSCT) by analyzing survival end points in defined groups of acute myeloid leukemia patients: A retrospective, multicenter Polish Adult Leukemia Group study. American Journal of Hematology. 2015; 90: 904-909.
31. Mizutani M, Hara M, Fujita H, et al. Comparable outcomes between autologous and allogeneic transplant for adult acute myeloid leukemia in first CR. Bone Marrow Transplant. 2016; 51: 645-653.
32. Mizutani M, Takami A, Hara M, et al. A Comparison of the Outcomes of Autologous and Unrelated-Donor Transplantation in Adult Intermediate-Risk Acute Myeloid Leukemia Patients in First Complete Remission. Biology of Blood and Marrow Transplantation. 2016; 22(3): S30-S31. doi:10.1016/j.bbmt.2015.11.298
33. Mizutani M, Takami A, Hara M, et al. Comparison of Autologous and Unrelated Transplants for Cytogenetically Normal Acute Myelogenous Leukemia. Biol Blood Marrow Transplant. 2017; 23: 1447-1454.
34. Kunacheewa C, Ungprasert P, Phikulsod P, et al. Comparative Efficacy and Clinical Outcomes of Haploidentical Stem Cell Transplantation to Other Stem Sources for Treatment in Acute Myeloid Leukemia and Myelodysplastic Syndrome Patients: A Systematic Review and Meta-Analysis. Cell Transplant. 2020; 29: 0963689720904965.
35. O'Dwyer KM. Optimal approach to T-cell ALL. Hematology. 2022; 2022: 197-205.
36. Alimoghaddam K, Jahani M, Mousavi S, et al. Allogeneic stem Cell Transplantation outcome in acute Lymphoblastic Leukemia Patients. International Journal of Hematology-Oncology and Stem Cell Research. 2012; 1-4.
37. Russell-Smith TA, Chadda S, Lereun C, et al. Systematic review and pooled analysis of survival outcomes in patients with relapsed or refractory B-cell acute lymphoblastic leukaemia who have undergone haematopoietic stem cell transplant. Eur Rev Med Pharmacol Sci. 2022; 26: 975-995.
38. Kopińska A, Węglarz P, Koclęga A, et al. Allogeneic Hematopoietic Stem Cell Transplantation for Relapsed/Refractory Acute Myeloid Leukemia: A Single-Centre Experience. Clinical Lymphoma Myeloma and Leukemia. 2023; 23: 28-39.
39. Evers G, Beelen DW, Braess J, et al. Outcome of Patients with Acute Myeloid Leukemia (AML) Undergoing Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) Beyond First Complete Remission (CR1). Blood. 2018; 132: 4649.
40. Montoro J, Balaguer-Roselló A, Sanz J. Recent advances in allogeneic transplantation for acute myeloid leukemia. Current Opinion in Oncology. 2023; 35: 564.
41. Leotta S, Condorelli A, Sciortino R, et al. Prevention and Treatment of Acute Myeloid Leukemia Relapse after Hematopoietic Stem Cell Transplantation: The State of the Art and Future Perspectives. J Clin Med. 2022; 11: 253.
42. Klyuchnikov E, Badbaran A, Massoud R, et al. Enhanced Immune Reconstitution of γδ T Cells after Allogeneic Stem Cell Transplantation Overcomes the Negative Impact of Pretransplantation Minimal Residual Disease-Positive Status in Patients with Acute Myelogenous Leukemia. Transplantation and Cellular Therapy. 2021; 27: 841-850.
43. Yang B, Yu R, Cai L, et al. Haploidentical versus matched donor stem cell transplantation for patients with hematological malignancies: a systemic review and meta-analysis. Bone Marrow Transplant. 2019; 54: 99-122.
44. McCurdy SR, Luznik L. How we perform haploidentical stem cell transplantation with posttransplant cyclophosphamide. Blood. 2019; 134: 1802-1810.
45. Jiang H, Hu Y, Mei H. Consolidative allogeneic hematopoietic stem cell transplantation after chimeric antigen receptor T-cell therapy for relapsed/refractory B-cell acute lymphoblastic leukemia: who? When? Why? Biomark Res. 2020; 8: 66.
46. Cai B, Guo M, Ai H. Microtransplantation: clinical applications and mechanisms. Curr Opin Hematol. 2018; 25: 417-424.

47. Pan B, Lazarus HM, Gale RP. Microtransplantation for Acute Myeloid Leukemia: A Systematic Review. JAMA Oncology. 2020; 6: 1614-1620.

48. Stokke JL, Bhojwani D. Antibody-Drug Conjugates for the Treatment of Acute Pediatric Leukemia. J Clin Med. 2021; 10: 3556.

49. Liu K, Li M, Li Y, et al. A review of the clinical efficacy of FDA-approved antibody–drug conjugates in human cancers. Mol Cancer. 2024; 23: 1-16.

50. Wei AH, Tiong IS. Midostaurin, enasidenib, CPX-351, gemtuzumab ozogamicin, and venetoclax bring new hope to AML. Blood. 2017; 130: 2469-2474.

51. Norsworthy KJ, Ko C, Lee JE, et al. FDA Approval Summary: Mylotarg for Treatment of Patients with Relapsed or Refractory CD33-Positive Acute Myeloid Leukemia. The Oncologist. 2018; 23: 1103-1108.

52. Cooper TM, Franklin J, Gerbing RB, et al. AAML03P1, a pilot study of the safety of gemtuzumab ozogamicin in combination with chemotherapy for newly diagnosed childhood acute myeloid leukemia: a report from the Children's Oncology Group. Cancer. 2012; 118: 761-769.

53. Gamis AS, Alonzo TA, Meshinchi S, et al. Gemtuzumab ozogamicin in children and adolescents with de novo acute myeloid leukemia improves event-free survival by reducing relapse risk: results from the randomized phase III Children's Oncology Group trial AAML0531. J Clin Oncol. 2014; 32: 3021-3032.

54. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: Final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. Cancer. 2019; 125: 2474-2487.

55. Bhojwani D, Sposto R, Shah NN, et al. Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. Leukemia. 2019; 33: 884-892.

56. O'Brien MM, Ji L, Shah NN, et al. Phase II Trial of Inotuzumab Ozogamicin in Children and Adolescents with Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia: Children's Oncology Group Protocol AALL1621. JCO. 2022; 40: 956-967.

57. Masters JC, Nickens DJ, Xuan D, et al. Clinical toxicity of antibody drug conjugates: a meta-analysis of payloads. Invest New Drugs. 2018; 36: 121-135.

58. Godwin CD, McDonald GB, Walter RB. Sinusoidal obstruction syndrome following CD33-targeted therapy in acute myeloid leukemia. Blood. 2017; 129: 2330-2332.

59. de Goeij BECG, Vink T, ten Napel H, et al. Efficient Payload Delivery by a Bispecific Antibody–Drug Conjugate Targeting HER2 and CD63. Molecular Cancer Therapeutics. 2016; 15: 2688-2697.

60. Walter RB. Brief overview of antibody-drug conjugate therapy for acute leukemia. Expert Opin Biol Ther. 2021; 21: 795-799.

61. Gugliotta G, Castagnetti F, Soverini S, et al. A Review and an Update of European LeukemiaNet Recommendations for the Management of Chronic Myeloid Leukemia. In: Hehlmann R, ed. Chronic Myeloid Leukemia. Springer International Publishing. 2021; 145-158.

62. Daver NG, Erba HP, Papadantonakis N, et al. A Phase I, First-in-Human Study Evaluating the Safety and Preliminary Antileukemia Activity of IMGN632, a Novel CD123-Targeting Antibody-Drug Conjugate, in Patients with Relapsed/Refractory Acute Myeloid Leukemia and Other CD123-Positive Hematologic Malignancies. Blood. 2018; 132: 27-27.

63. Gökbuget N, Boissel N, Chiaretti S, et al. Management of ALL in adults: 2024 ELN recommendations from a European expert panel. Blood. 2024; 143: 1903-1930.

64. Gökbuget N, Kneba M, Raff T, et al. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. Blood. 2012; 120: 1868-1876.

65. Zhang M, Huang H. How to Combine the Two Landmark Treatment Methods-Allogeneic Hematopoietic Stem Cell Transplantation and Chimeric Antigen Receptor T Cell Therapy Together to Cure High-Risk B Cell Acute Lymphoblastic Leukemia? Front Immunol. 2020; 11: 611710.

66. Diorio C, Maude SL. CAR T cells vs allogeneic HSCT for poor-risk ALL. Hematology. 2020; 2020: 501-507.

67. Qiu Y, Wan CL, Xu MZ, et al. Safety and efficacy of CD22 and CD19 CAR-T bridging auto-HSCT as consolidation therapy for AYA and adult B-ALL. Blood Cancer J. 2023; 13: 66.

68. Liu Z, Wu T, Song Y, et al. Good Survival of CAR-T Cell Therapy Bridging to Allo-HSCT for Relapsed/Refractory Ph-Positive B-Cell Acute Lymphoblastic Leukemia. Blood. 2023; 142: 7043.

69. Pretelli G, Mati K, Motta L, et al. Antibody-drug conjugates combinations in cancer treatment. Explor Target Antitumor Ther. 2024; 5: 714-741.

70. Hills RK, Castaigne S, Appelbaum FR, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. Lancet Oncol. 2014; 15: 986-996.

71. Marei HE, Cenciarelli C, Hasan A. Potential of antibody–drug conjugates (ADCs) for cancer therapy. Cancer Cell International. 2022; 22: 255.

72. Valent P, Bauer K, Sadovnik I, et al. Cell-based and antibody-mediated immunotherapies directed against leukemic stem cells in acute myeloid leukemia: Perspectives and open issues. STEM CELLS Translational Medicine. 2020; 9: 1331-1343.

73. García-Alonso S, Ocaña A, Pandiella A. Resistance to Antibody-Drug Conjugates. Cancer Res. 2018; 78: 2159-2165.

74. Díaz-Rodríguez E, Gandullo-Sánchez L, Ocaña A, et al. Novel ADCs and Strategies to Overcome Resistance to Anti-HER2 ADCs. Cancers (Basel). 2021; 14: 154.

75. Mu H, Zhu X, Jia H, et al. Combination Therapies in Chronic Myeloid Leukemia for Potential Treatment-Free Remission: Focus on Leukemia Stem Cells and Immune Modulation. Front Oncol. 2021; 11: 643382.

76. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. New England Journal of Medicine. 2020; 383: 617-629.

77. Bhansali RS, Pratz KW, Lai C. Recent advances in targeted therapies in acute myeloid leukemia. Journal of Hematology & Oncology. 2023; 16: 29.

78. Daver N, Montesinos P, Aribi A, et al. Broad Activity for the Pivekimab Sunirine (PVEK, IMGN632), Azacitidine, and Venetoclax Triplet in High-Risk Patients with Relapsed/ Refractory Acute Myeloid Leukemia (AML). Blood. 2022; 140: 145-149.

79. Debureaux PE, Labopin M, Mamez AC, et al. Fractionated gemtuzumab ozogamicin in association with high dose chemotherapy: a bridge to allogeneic stem cell transplantation in refractory and relapsed acute myeloid leukemia. Bone Marrow Transplantation. 2020; 55: 452-460.

80. Russell NH, Wilhelm-Benartzi C, Othman J, et al. Fludarabine, Cytarabine, Granulocyte Colony-Stimulating Factor, and Idarubicin with Gemtuzumab Ozogamicin Improves Event-Free Survival in Younger Patients with Newly Diagnosed AML and Overall Survival in Patients with NPM1 and FLT3 Mutations. J Clin Oncol. 2024; 42: 1158-1168.

81. Mosna F. The Immunotherapy of Acute Myeloid Leukemia: A Clinical Point of View. Cancers. 2024; 16: 2359.

82. Thol F, Ganser A. Treatment of Relapsed Acute Myeloid Leukemia. Curr Treat Options Oncol. 2020; 21: 66.

83. Nannya Y, Viswabandya A, Lu P. Advances in Allogeneic Hematopoietic Stem Cell Transplantation for Acute Leukemia. Blood Cell Ther. 2022; 5: S25-S33.