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CELLULAR AND MOLECULAR TECHNOLOGIES IN THE TREATMENT OF RELAPSED ACUTE LEUKEMIA IN CHILDREN

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ABSTRACT
The review analyzes current concepts of relapsed acute lymphoblastic leukemia in children, with an emphasis on the clinical and biological features of the disease and the role of minimal residual disease in predicting relapse. The possibilities and limitations of standard chemotherapy, molecularly targeted approaches, and immunotherapy are considered, including bispecific antibodies and CAR-T-cell technologies. It is shown that despite the high rate of initial responses, treatment resistance, toxicity, and antigen escape remain the main causes of treatment failure. The review concludes that personalized strategies combining molecular diagnostics and innovative therapeutic methods are needed to improve long-term outcomes in children with relapsed ALL.

KEYWORDS: acute lymphoblastic leukemia, children, disease relapse, minimal residual disease (MRD), immunotherapy, CAR-T-cell therapy.

INTRODUCTION
To date, acute lymphoblastic leukemia (ALL) remains the leading malignant tumor of childhood and accounts for the main oncohematological burden in children, with the highest incidence occurring in the early preschool period, which makes this problem especially significant for pediatrics. According to international registries, approximately 80,000–90,000 new cases of ALL are diagnosed annually in children worldwide [27], while in the Russian Federation the incidence rate remains stable at an average of 3–4 cases per 100,000 children, despite the introduction of modern treatment protocols [1]. Significant progress in survival has been achieved through multi-agent chemotherapy; however, relapsed forms of the disease continue to determine an unfavorable prognosis and high mortality. In recent years, the focus has shifted from morphological control of remission to molecular cloning of minimal residual disease (MRD), which has made it possible to gain a deeper understanding of relapse biology and early mechanisms of drug resistance [2–5].
Despite active research into MRD-oriented strategies, a considerable proportion of patients with molecular relapse continue to progress, which highlights the limitations of existing approaches [8]. In this context, immunotherapy, primarily CAR-T-cell technologies, has become a fundamentally new stage in the treatment of relapsed acute leukemia in children, demonstrating high rates of initial response. However, accumulated clinical experience has shown that even after achieving deep remission, the risk of repeated relapse persists, associated both with antigen loss and functional exhaustion of CAR-T cells [10]. Many authors have described individual aspects of MRD monitoring, allogeneic transplantation, and CAR-T therapy in detail, but a unified effective strategy capable of ensuring long-term disease control has not yet been developed. Thus, the problem of relapsed ALL in children remains unresolved and requires a comprehensive analysis of current data combining molecular diagnostics and innovative treatment methods [12–18]. In this regard, this topic retains high scientific and clinical relevance.
The aim of this review is to analyze current strategies for combating relapsed acute leukemia in children, from MRD cloning to the use of CAR-T-cell therapy, with an assessment of their possibilities, limitations, and prospects for further development.

Epidemiology and Clinical-Biological Features of Relapsed Acute Leukemia in Children
Acute lymphoblastic leukemia remains the most common malignant disease in children, and according to international and national oncohematological registries, tens of thousands of new cases are diagnosed worldwide each year, accounting

for a significant proportion of all pediatric oncological pathology [19]. Although the introduction of risk-adapted protocols has made it possible to achieve long-term survival in more than 80–85% of patients, disease relapse still occurs in 10–15% of children, sharply worsening the prognosis and reducing overall survival to below 50%, while in refractory disease it falls to critically low levels [28]. According to clinical observations and multicenter studies, relapsed disease remains one of the leading causes of mortality in pediatric oncohematological disorders [21].

Analysis of the clinical and biological features of relapsed ALL shows that the disease is initially polyclonal, and disease recurrence is more often associated not with the emergence of a fundamentally new clone, but with the expansion of minor subclones that were already present at the stage of initial diagnosis [25–28]. Studies devoted to molecular profiling of relapses have shown that in approximately half of cases, relapse develops from a previously low-abundance clone, while in some patients a mixed or polyclonal pattern of disease recurrence is detected. Unfavorable cytogenetic variants and the accumulation of mutations in genes associated with regulation of treatment response and the cell cycle, including TP53, NRAS, CREBBP, and NT5C2, have substantial prognostic significance, as confirmed by both clinical data and experimental models [29].

Several studies emphasize that the clones responsible for relapse possess marked drug resistance and biological features of "stemness," including chromatin remodeling and changes in energy metabolism, which explains the low effectiveness of standard chemotherapy [30–32]. Thus, relapsed acute leukemia in children should be regarded not merely as a return of the disease, but as a biologically and clinically distinct condition formed under therapeutic pressure. This determines the need to search for new diagnostic markers, more accurate assessment of minimal residual disease, and the development of personalized treatment strategies.

Minimal Residual Disease (MRD) as a Key Tool for Risk Stratification and Relapse Monitoring

Minimal residual disease is currently recognized as a key prognostic indicator in acute lymphoblastic leukemia in children; however, its clinical interpretation remains a matter of debate [33–35]. On the one hand, numerous studies demonstrate that MRD-negative status after induction or consolidation therapy is associated with higher survival, as emphasized by S.E. Siegel et al., who consider MRD an integral reflection of tumor sensitivity to treatment. On the other hand, data from N. Gökbuget et al. indicate that identical MRD levels determined by different methods do not always have comparable prognostic value, which limits the universality of this indicator [36]. The introduction of highly sensitive molecular technologies and next-generation sequencing has made it possible to identify the complex clonal structure of the disease; however, it remains unclear which specific subclones should be considered clinically significant when making therapeutic decisions. A number of authors emphasize that molecular MRD reflects not only the volume of residual tumor, but also its biological properties, including drug resistance; nevertheless, clear threshold values of risk have not yet been standardized. K.M. Cappell and J.N. Kochenderfer show that even after achieving MRD-negative status following CAR-T therapy, some patients experience late relapses, which calls into question the absolute prognostic significance of MRD as a single indicator [37–40]. As a result, minimal residual disease remains an indispensable monitoring tool, but its use as the sole criterion for risk stratification requires a cautious approach and consideration of the clinical context, disease biology, and treatment methods used [41].

Modern Chemo- and Targeted Approaches in the Treatment of Relapsed Acute Leukemia

Although overall survival in children with acute lymphoblastic leukemia is currently impressive, data from large international cohorts show that, in relapse, the effectiveness of standard intensified chemotherapy quickly reaches its limit, especially in patients with unfavorable molecular subtypes and repeated relapses [42]. Against this background, the introduction of targeted approaches has become a logical step, where inhibitors of signaling pathways — primarily ABL-, FLT3-, and JAK-dependent cascades — are used not as an "addition," but as an attempt to achieve biological control of the disease. This is confirmed by the results of multicenter studies in patients with Ph+ and Ph-like ALL [43]. However, critical analysis shows that the success of ABL inhibitors, including imatinib and dasatinib, is largely limited to specific subgroups and does not automatically translate to T-ALL or genetically heterogeneous relapse variants, where the frequency of primary and secondary resistance remains high (Hay et al., 2019). Similarly, the use of FLT3 and MEK inhibitors remains fragmented and in most cases is based on early-phase clinical trials, which does not yet allow them to be considered a full alternative to intensive chemotherapy or transplantation [44–48]. A significant limitation of current targeted strategies remains the toxicity of combinations and the lack of long-term quality-of-life data, which is especially critical in the pediatric population and is emphasized in registration and real-world clinical reports on cellular and targeted therapy [39]. In this context, the data presented in the table make it possible to clearly compare intensified chemotherapy regimens and molecularly targeted approaches, identifying not only the therapeutic advantages of individual inhibitors, but also the systemic gaps that still limit their broad use in relapsed acute leukemia [50].

Table 1. Current Chemo- and Targeted Approaches in Relapsed ALL in Children.

Therapeutic approach	Molecular target / mechanism	Main drugs	Clinical context of use	Potential advantages	Key limitations
Intensified chemotherapy	Non-specific DNA damage and inhibition of cell division	VPLD, ALLR3, BFM	First and repeated relapses of ALL	Rapid reduction of tumor burden	High systemic toxicity; limited effect in resistant disease

		modifications			
ABL-directed tyrosine kinase inhibitors	BCR::ABL1 and ABL-class rearrangements	Imatinib, dasatinib, ponatinib	Ph+ ALL and ABL-class Ph-like ALL	Significant improvement in survival without HSCT	Development of mutational resistance and vascular risks
JAK/STAT inhibitors	Activation of the JAK/STAT signaling pathway	Ruxolitinib	Ph-like ALL with CRLF2/JAK alterations	Biologically justified targeted effect	Lack of long-term clinical data
Proteasome inhibitors	Disruption of protein degradation and induction of apoptosis	Bortezomib, carfilzomib, ixazomib	Relapsed B- and T-ALL	Increased sensitivity to chemotherapy	Neurotoxicity and heterogeneous response
BH3 mimetics	Blockade of anti-apoptotic proteins of the BCL-2 family	Venetoclax, navitoclax	Chemorefractory and molecularly unfavorable forms	Efficacy in profound drug resistance	Myelosuppression and risk of infections
MEK inhibitors	Inhibition of the RAS/RAF/MEK/ERK cascade	Selumetinib, trametinib	ALL with RAS-pathway mutations	Targeted intervention in oncogenic signaling	Early stages of clinical evaluation

Thus, the possibilities of chemo- and targeted therapy remain limited due to resistance and toxicity. This justifies the transition to the analysis of immunotherapy as the next stage in the evolution of treatment for relapsed acute leukemia.

Immunotherapy in Relapsed Acute Leukemia: Bispecific Antibodies and New Immune Strategies

Despite the high overall cure rate of pediatric ALL, relapsed and refractory forms remain the main cause of treatment failure, which has shifted the focus of research toward immunotherapy as an alternative to repeated intensified chemotherapy [27]. Recent studies have shown that bispecific antibodies, primarily blinatumomab, provide a qualitatively different type of antitumor response by directly engaging the patient's T cells and bypassing some mechanisms of drug resistance typical of cytostatic agents. At the same time, clinical series and registry-based observations demonstrate that the benefit of blinatumomab is most pronounced in patients with low tumor burden and MRD-positive status, whereas in cases of massive disease involvement its effect may be limited by toxicity and rapid exhaustion of the T-cell pool [30–35]. Inotuzumab, which targets CD22, has expanded treatment options for patients with CD19 loss; however, its use has revealed a new problem: pronounced hepatotoxicity and the risk of veno-occlusive disease, especially in the setting of subsequent transplantation. A number of authors emphasize that resistance to immunotherapy develops not only through antigen loss, but also through immune mechanisms, including checkpoint expression and expansion of regulatory T cells, which reduces the duration of response [37–39]. Thus, current data indicate that the efficacy of bispecific antibodies is determined by a complex balance between tumor biology and the state of the patient's immune system, and that no universal solution exists for all forms of relapse. In this context, immunotherapy in relapsed acute leukemia is considered not as a replacement, but as a flexible tool within a multistage treatment strategy requiring precise patient selection and thoughtful integration with transplantation and other immune approaches.

CAR-T-cell therapy in the treatment of relapsed and refractory acute leukemia in children

Acute lymphoblastic leukemia in children remains the leading oncological disease of childhood; however, relapsed and refractory forms constitute the main area of therapeutic failure, despite the progress achieved in frontline treatment [38, 58]. The substantial improvement in overall survival in standard B-ALL contrasts with the unfavorable prognosis of r/r B-ALL, where intensive chemotherapy protocols and hematopoietic stem cell transplantation are associated with high toxicity and limited long-term efficacy. In this context, CAR-T-cell therapy has fundamentally changed the therapeutic paradigm by providing a high rate of deep MRD-negative remissions through targeted elimination of CD19-positive leukemic clones and prolonged persistence of effector T cells in vivo [42–46]. The clinical efficacy of CAR-T therapy is particularly significant in patients resistant to antibody-based immunotherapy and conventional reinduction regimens, which emphasizes its role as an independent therapeutic approach rather than only an auxiliary strategy. At the same time, the therapeutic potential of CAR-T is limited by acute immune complications, including cytokine release syndrome and neurotoxicity, as well as by the phenomenon of antigen escape, leading to CD19-negative relapses. The role of CAR-T as a "bridge" to allogeneic transplantation remains critically important, since accumulated clinical data indicate heterogeneous outcomes: some patients achieve long-term remission without HSCT, whereas in others the absence of consolidation is associated with an increased risk of late relapse [50–52]. Thus, further development of CAR-T therapy in pediatric oncohematology requires optimization of receptor constructs, implementation of multi-antigen strategies, and more accurate patient stratification based on the molecular profile of the disease and MRD dynamics.

Unresolved Problems and Prospects for the Development of Personalized Treatment Strategies

Despite the impressive clinical progress achieved in the treatment of relapsed and refractory acute lymphoblastic leukemia, resistance to therapy remains one of the key unresolved problems, since even with high initial response rates a significant proportion of patients experience loss of remission [59]. Current data indicate that relapse is often caused by antigen escape and functional exhaustion of CAR-T cells, which limits the duration of the antitumor effect and requires reconsideration of single-target approaches [53]. In this context, the development of multi-target CAR-T constructs is regarded as a logical step toward reducing selective pressure on the tumor; however, clinical results show that even dual targeting does not fully overcome the biological heterogeneity of the disease. Additional difficulties are related to the choice of an optimal strategy after remission is achieved, since combining CAR-T therapy with allogeneic hematopoietic stem cell transplantation may improve disease control in high-risk patients, but at the same time increases the likelihood of transplant-related toxicity and does not always result in an overall survival benefit [54–56]. This emphasizes the need to move away from universal algorithms toward individualized decisions based on the dynamics of minimal residual disease, CAR-T-cell persistence, and the clinical and biological characteristics of the patient. The prospects for further development of personalized treatment strategies are associated with a deeper understanding of resistance mechanisms, including epigenetic changes and T-cell exhaustion programming, which shifts the focus of research toward optimizing the quality of the immune response [57]. In parallel, new technological approaches are actively developing, such as allogeneic and rapid CAR-T platforms, which can expand access to therapy and shorten the waiting time for treatment, although their long-term safety and efficacy still require confirmation. Taken together, these directions form a transition from the concept of "one solution for all" to a truly personalized treatment model, in which the choice of therapeutic strategy is determined by the biology of the disease rather than only by stage or the number of previous lines of therapy.

CONCLUSION

The review examines the main clinical and biological features of relapsed acute lymphoblastic leukemia in children, as well as the role of minimal residual disease in predicting and monitoring the course of the disease. It is shown that standard chemo- and targeted approaches, despite the progress achieved, are often insufficiently effective in relapse, which has led to the active introduction of immunotherapy and CAR-T-cell technologies. At the same time, accumulated data indicate that even modern methods do not always ensure long-term disease control due to resistance, antigen escape, and treatment toxicity. In this context, the results of the review emphasize the practical significance of searching for personalized strategies that combine molecular diagnostics and innovative therapeutic methods as an important direction for further improving outcomes in children with relapsed ALL.

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