Chapter 4

Immunotherapy in Pediatric Acute Leukemia: A Novel Magic Bullet or an Illusory Hope?

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Additional information is available at the end of the chapter

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Abstract

The last decade became the renaissance for investigating and exploring the potential role of immunotherapy in pediatric acute leukemia (AL). It is beyond question that there is an interaction between innate immune system and hematological malignancy. Leukemia cells inhibit the host immune response according to multiple mechanisms, but exploiting the innate immune system mechanisms can overcome the resistance to the conventional treatment. What is the role of immunotherapy in pediatric AL treatment? Does it have the potential to substitute or combine the standard chemotherapy? What is the best possible timing to take advantage of immune interventions? This review is considered to follow through the possible treatment options including their foundation, strong and weak points, but also information about possible implementation into the clinical practice.

Keywords: immunotherapy, acute lymphoblastic leukemia, acute myeloblastic leukemia, children

1. Introduction

Acute leukemia (lymphoblastic and myeloblastic) is the most common malignancy diagnosed in children with an incidence of about 4.2 and 4.9 per 100,000 in the age groups of 0–19 and 0–14, respectively. In the population of children aged 0–19, acute lymphoblastic leukemia (ALL) accounts for approximately 75% while acute myeloblastic leukemia (AML) accounts for 20% of pediatric leukemia cases. Contemporary therapy allows achieving complete remission in approximately 90% of patients with ALL and 70% with AML [1, 2]. It is worth mentioning that 50 years ago acute leukemia was almost universally incurable [3]. The breakthrough has been achieved through standardized and optimized multi-agent therapeutic regimens and through therapy individualization according to the risk stratification. However, even though
great progress in therapy is reported, refractory or relapsed leukemia remains one of the major
dates of cancer-related mortality. Failure to respond to chemotherapy is almost universally
connected with poor prognosis. Survival rates for patients with relapsed or refractory AML
receiving a second treatment attempt was estimated between 25 and 30% [4]. In 15% of ALL
patients who experience relapse of the disease, long-term survival rates vary from 40 to 50%,
even though the remission is achieved in over 70% of patients [5, 6]. What is more, current che-
motherapy regimens are consisted of very intensive blocks of treatment that are responsible
for multiple acute and long-term sequelae, especially in the pediatric population. According to
multiple research, 60% of children after an anticancer treatment present at least one organ late
effect [7]. New approaches that redirect treatment toxicity accurately to the neoplastic cells,
sparing the normal cells and hematopoietic counterparts, will significantly reduce the possible
complications and improve the survivor’s quality of life.

1.1. Contemporary treatment strategy for acute leukemia in children

The therapy for ALL and AML in children is based on standardized protocols and is com-
posed of four major phases: remission induction, followed by consolidation, reinduction
(intensification), and maintenance. In order to provide the most effective and harmless treat-
ment for every patient, children are classified into three groups based on the risk of treatment
failure (standard, intermediate, or high). This way, less toxic regimens can be administered
to patients with more favorable prognosis, whereas those children with features showing
higher risk of relapse are receiving more aggressive blocks of chemotherapy. Protocols that
are currently used in treatment of acute leukemia in Polish children are ALL IC-BFM 2009 and
AML-BFM 2012 [8, 9]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT), which
is a form of immunotherapy, is generally not recommended in the first remission of pediatric
AML patients except for those at high risk. Comparably, only the children with high-risk ALL
and additional particular unfavorable prognostic factors, like T-cell ALL, high initial leuko-
cytosis, hypodiploidy, and genetic impairments, like t(9;22) or t(4;11), benefit from allo-HSCT
in the first complete remission [10, 11]. Radiotherapy is considered as a treatment option in
case of extramedullary organ (central nervous system, testicular) involvement, but also as
a prevention of central nervous system relapse in every patient with AML and, in strictly
defined circumstances, children with the high-risk ALL. This approach is reserved only for
selected group of patients according to an increased risk and severity of ionization-related
late sequelae in the pediatric population [12].

Chemotherapy regimens used in acute leukemia in children are distinguished as extremely
intensive, especially the treatment in patients with AML. This causes a long period of bone
marrow aplasia that causes vulnerability to numerous infectious complications. Notably,
5% of treatment failures using previous versions of chemotherapy regimens were the
result of treatment-related deaths in the first complete remission. According to the significant
improvement in supportive care and therapy individualization, the treatment-related
mortality has decreased gradually over the last decade [13]. However, there are still patients
with drug-resistant or recurrent leukemia who require further efforts to identify effective
treatment strategies based on the advances in our knowledge, understanding of leukemic cell
biology, and interactions between them and the innate immune system. Without searching
for new approaches and confining ourselves only to chemotherapy regimens, their prognosis remains unfavorable.

1.2. Rationale for immunotherapy in acute leukemia

The evidence supporting the idea of interactions between immune system and malignant cells is based on multiple observations of leukemia course depending on immune system function. For example, shift reconstitution of the immune system after induction regimens correlates with improved survival, and absolute leukocyte count is an independent prognostic factor for survival in patients with acute leukemia [14]. What is more, it is proven that malignant cells use multiple pathways to interfere the host immune system promoting the number and function of regulatory T cells (T regs) and subsequently reducing the ability of cytotoxic T cells to target leukemia [17].

The most popular and the only undisputed and thoroughly investigated form of immunotherapy, which has been applied in clinical practice for a few decades, is **allogeneic HSCT**. This form of treatment is considered in a subgroup of high-risk patients in the first remission or in refractory and relapsed hematological malignancies. The **graft-versus-leukemia effect (GvL)**, which occurred to be an additional immunological benefit to this approach, is mediated by donor T cells and natural killer (NK) cells against residual leukemia blasts. This phenomenon was discovered according to the observations of a decreased risk of relapse in allogeneic graft recipients compared to patients after syngeneic HSCT or those who received T-depleted grafts to reduce the risk of graft-versus-host-disease (GvHD) [15].

Understanding the impact on immune response against malignant cells was a trigger to further investigations that enabled a better understanding of mechanisms of how leukemia cells manage to evade immune surveillance. This study has laid the foundation for novel approaches using immune interventions. Immunotherapy approaches are mostly investigated in the context of HSCT. However, possible strategies are feasible also in settings which are not related to transplantation. The next chapter indicates the immunotherapeutic approaches that can be potentially implemented into the treatment regimens of acute leukemia in children (Table 1).

| To boost the immunity                          | Inhibiting excessive function of regulatory T cells | CTLA-4 inhibition: Iipilimumab |
|                                               |                                                    | PD-1 inhibition: Nivolumab     |

| To enhance the cytotoxic effect               | Using T cells, NK cells, and dendritic cells      | Allogeneic HSCT               |
|                                               |                                                    | Donor lymphocyte infusion (DLI) |
|                                               |                                                    | CAR-T cell therapy             |
|                                               |                                                    | Transfer of allogeneic NK cells |
|                                               |                                                    | CAR-engineered NK cell therapy |
|                                               |                                                    | Dendritic cell (DC) vaccines   |

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To boost the immunity: potential therapies inhibiting excessive function of regulatory T cells

Regulatory T cells’ (T reg, CD4+, CD25+) major role is to control immune tolerance. They are crucial to maintain unresponsiveness against self-antigens, but also to prevent autoimmune diseases and allogeneic graft rejection. In terms of their role in hematological malignancies, they may suppress the anticancer effect mediated by activated T cells. As a consequence of tumor activity, their immunosuppressive effect on T cells may be aggravated compared to healthy individuals (Figure 1). Studies show that high plasma and tissue T regs level at the moment of diagnosis correlate with a worse response to chemotherapy and prognosis [16].

One of the mechanisms that leukemia cells tend to interfere T regs function is overexpression of the FOXP3 gene and high levels of Foxp3 mRNA, which is considered to be essential for their inhibitory effect. This phenomenon was described in particular subtypes of AML [17], but there are a few reports of Foxp3 overexpression and T regs activity in ALL. However, it

Table 1. Immunotherapeutic strategies in acute leukemia.

| To bridge the tumor cell to the killer |
|---------------------------------------|
| Monoclonal antibodies                  | Anti-CD20: Rituximab, Ofatumumab |
|                                       | Anti-CD22: Epratuzumab             |
|                                       | anti-CD52: Alemtuzumab             |
|                                       | anti-CD33: Lintuzumab              |
| Monoclonal antibodies conjugated to cytotoxic compounds | Anti-CD22 linked to calicheamicin: Inotuzumab ozogamicin |
|                                       | Anti-CD33 linked to calicheamicin: Gemtuzumab ozogamicin |
| Bispecific T-cell engagers (BiTEs)     | Blinatumomab, anti-CD3, and -CD19 |

Figure 1. Immune surveillance evasion of leukemic blasts by promoting T regs–inhibitory function.
has been described that B-ALL patients’ Tregs presented higher immunosuppression than T reg cells from normal healthy individuals. What is more, chemotherapy corresponded to the reduction of Foxp3 and interleukin-10 expression which is also a mediator of cytotoxic T cells suppression [18, 19].

Another way to support inhibitory Tregs function mediated by leukemic blasts is the expression of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) on T cells and the surface of leukemia cells. CTLA-4 binds the ligands which are essential for early T cell activation (CD80 and CD86) and as a result it inhibits T cell activation and increases inhibitory cytokine production by Tregs. It has been proved that the higher levels of soluble CTLA-4 and CD86 in B-ALL patients worsen the prognosis and should be considered as potential high-risk factors [20, 21]. Inhibition of CTLA-4 by specific antibody ipilimumab was not yet investigated in acute leukemia in children, but there are ongoing clinical trials assessing its potential in small groups of adults with acute myeloid leukemia, relapsed after allo-HSCT showing promising regression of malignancy, but also immune-related adverse events connected with drug infusion [22–24].

Programmed cell death protein 1 (PD-1) high expression on activated immune system cells and Programmed cell death ligand 1 (PD-L1) on blasts due to the tumor influence are mechanisms for leukemia evasion from an immune attack. This molecule induces T cell tolerance by direct inhibition of activated T cells and enhancement of Tregs—inhibitory function in myeloid malignancies. Exhausted T cells are no longer capable to produce the cytokines: interleukin 2 (IL-2), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), which impair their cytotoxic effect. This is also the signal to induce the apoptosis of activated T cells. Overexpression of PD-1 is associated with leukemia relapse after hematopoietic stem cell transplantation [25]. Using PD-1 is being investigated as its inhibition (nivolumab) may have the potential to break immune tolerance to AML cells. It may also enhance the cytotoxic effect of donor-derived cytotoxic T cells [26–28].

1.4. To enhance the cytotoxic effect: potential therapies are promoting innate or using adoptive T cells, NK cells, and dendritic cells

Donor lymphocyte infusion is the basic method of the relapse treatment and prevention after allogeneic HSCT mediated through the GvL effect. Its major complication was the high risk of graft-versus-host-disease, which is associated with a donor lymphocyte reaction against host antigens [29]. Its efficacy is nonetheless assessed as disappointing. A major obstacle is tumor-mediated evasion from the immune surveillance by downregulating surface antigens and costimulatory molecules (CD80 and CD86). As a result, T cells are not appropriately activated in vivo to induce an antitumor response. To improve the efficacy of DLI, multiple methods have been used: costimulation with CD3/CD28 and activation ex vivo [30], enrichment of donor T cells with leukemia-specific antigens (WT1) [31] or tumor-specific and host-restricted minor histocompatibility complex antigens [29, 32].

The DLI and GvL effect were the foundation to search for modified approaches to avoid side effects and use the potential T cells against leukemia. The next step was using genetically modified and activated autologous T cells to target tumor-specific antigens. The major advantage of this approach is eliminating the risk of GvHD.
At first, genetic modifying was based on transferring α/β heterodimer of T-cell receptors (TCRs) to the autologous T cells, but the limitation was the fact that the TCR receptor was only able to recognize antigens presented by human leukocyte antigen (HLA) molecules, which can be downregulated on the tumor cells avoiding immune surveillance. The next idea was to transfer chimeric antigen receptors (CARs) instead that are composed of a single-chain-variable fragment (scFv) antibody, which is specific for tumor antigens. CARs have an ability to recognize and fight the cells presenting any specific antigen without HLA molecules. The engineered cells express antigen receptors against tumor-associated surface antigens, thus redirecting the effector cells and enhancing tumor-specific immunosurveillance [33].

**CAR-T cell therapy** is now being actively investigated in refractory or relapsed ALL in adults and children. At the moment, majority of patients benefit from this approach having achieved remission when the disease appears to be incurable in terms of using standard chemotherapy. Side effects are mostly immune-related and reversible. The studies were carried out on small groups of patients, and the results are now to be confirmed in the larger multicenter trials [34, 35].

The potential limitation that make a CAR-T therapy ineffective in some groups of patients is the lack of the antigens that would be specific only for leukemia cells and their ability to downregulate the antigens by the neoplastic cells, but also unsatisfactory persistence of CAR-T cells after an adoptive transfer and predominance of an immunosuppressive microenvironment, which is a result of leukemia and the host immune system interactions [36].

One of the major challenges in terms of defining the ideal CAR-T target antigen is identifying a leukemia-specific molecule, expressed primarily, if not exclusively on the neoplastic cells, absent on their normal hematopoietic counterpart. This is an important field of research in terms of immunotherapy efficacy improvement [37]. The antigen that is commonly used as a target against B-linear blasts is CD19; however, this molecule is not a specific one. Another target that is being currently evaluated in a context of CAR-T therapy in ALL is CD22. Targeting CD22 turned out to be effective in vitro and is currently investigated in vivo, but its expression is still not limited to leukemia cells as this antigen is naturally presented by HLA class I on dendritic cells (DCs) and macrophages [38, 39]. In AML, CD33 is one of the most popular among various antigens that are being investigated. However, it is highly expressed on both leukemic cells and their normal hematopoietic counterpart which explains the severe toxicity of immunotherapy targeting CD33 established in the clinical trials [40]. CD123 molecule has emerged as more specific for AML blasts as it is expressed at low levels by normal progenitor cells, which makes it more applicable [41]. There is no defined target that could be addressed in the treatment of T-linear ALL, which has a worse prognosis in the pediatric population compared to the B-linear analog.

Further investigations led to multiple improvements of the method, like producing NK CAR cells as an alternative to T cells [42, 43], enhancing cytotoxicity of CAR-T cells by the addition of costimulatory molecules (second and third generation) or by adding chemokine receptors to enable the effective infiltration to the tumor site. For example, the expression of CD40 ligand by genetically modified T cells leads to increased proliferation and secretion of proinflammatory TH1 cytokines, but also enhances the immunogenicity of tumor cells by upregulation of costimulatory molecules (CD80 and CD86), adhesion molecules (CD54, CD58, and CD70),
and human leukocyte antigen molecules on their surface. Improved survival was confirmed on a model with mice [44]. In terms of managing cytokine release syndrome, the researchers work on the antibody-based switches to mediate the interaction between the CAR-T cell and target cells to improve the safety of therapy [45].

In terms of using NK cells in the treatment of leukemia, a possible strategy is using adoptive transfer of allogeneic NK cells or genetically modified autologous NK cells (CAR-engineered NK cells). Supremacy of NK cells over T cells is connected with its lower potential to cause GvHD while being donor-derived [46, 47]. The limitation in using autologous NK cells is the overexpression of killer immunoglobulin-like receptors (KIRs) on target cells which counteract the activation of the NK cells and tumor lysis. To overcome this problem, it is more accurate to use allogeneic NK cells, but it is also important to examine the donor and recipient in terms of incompatibility of the KIR ligand (which is presented with HLA-Bw4 and HLA-C) [48]. Only mismatched donor’s NK cells would be effective in the treatment of residual disease. The efficacy of using adoptive immunotherapy with NK cells is being examined in AML patients who are not eligible for stem cell transplantation. The results indicate that this approach can help to sustain the remission in patients with AML, but its efficacy is limited in active disease and it was only examined in a small group of elderly patients [46]. There are no reports in applying the therapy in patients with ALL.

Eliciting the T cells immunity can also be performed by using dendritic cell vaccines, which are modified to present antigens that are characteristic for leukemia blasts. This way, cytotoxic T cells are activated to kill tumor cells overcoming the mechanisms of evading immune surveillance, like downregulating of surface antigens and then T regs function enhancement are present. DCs can be autologous or allogeneic, but the HLA restriction is essential for the second option. The specific antigen that has been used so far is Wilms’ Tumor-1 (WT1), which is a characteristic for myeloblasts, especially in relapse, but it is also detectable in some patients with ALL and different solid tumors. This approach was assessed as effective in several patients with posttransplant-relapsed AML or ALL. The GvHD was assessed as mild and no serious adverse events were reported [49–51]. Ongoing clinical trials are developed to assess WT1 dendritic cell vaccines in larger groups of patients.

1.5. To bridge the tumor cell to the killer

Antigens expressed on leukemic blasts can also be utilized as a target for specific antibodies. Hematological malignancies express surface molecules that are accessible in the circulation. Epitopes presented exclusively on leukemic cells would be preferential for the antibody therapy. However, identifying unique ones, characteristic only for the neoplastic cells and not for their normal hematopoietic counterparts, is challenging. There are several mechanisms that can be used to eliminate blasts including internalization of toxins or drugs that are conjugated to the antibodies, antibody-dependent cellular toxicity (ADCC), complement-dependent cytotoxicity (CDC), induction of apoptosis, and direct-engaging endogenous T cells at the leukemic cells surroundings. Antigens that are candidates for antibody therapy in ALL are mostly characteristic for B-linear differentiation, like CD19, CD20, and CD22, but it is necessary to look for the targets not only presented on B-linear blasts, like CD52. Epitope that is targeted in AML is CD33 [52].
Monoclonal antibodies (MoAbs) are capable of eliminating blasts not only by promoting cytotoxic or complement-dependent cell lysis but also by blocking the effects that are advantageous for neoplastic cells, mediated by growth signals and various agonists. They are selective to the targeted molecules so that the treatment-related toxicity can be reduced. Also, the treatment response can be improved by using monoclonal antibodies as they sensitize leukemic blasts to the conventional chemotherapy. Their efficacy is generally limited when employed as a single agent, but in combination with the standard regimens they improve the overall survival even in chemoresistant or posttransplantation-relapsed patients [53, 54].

CD20 was the first epitope that was successfully applied in the therapy of hematological malignancies. Rituximab is a chimeric monoclonal antibody, approved in 1997 by the Food and Drug Administration (FDA) in the treatment of non-Hodgkin’s lymphoma and chronic lymphocytic leukemia, but its efficacy is also being assessed in combination with chemotherapy in adults with B-cell acute lymphoblastic leukemia. In several studies, targeting CD20 was related to obtaining a prominent improvement of chemotherapy results in the Philadelphia chromosome-negative BCP-ALL [55–57]. Ofatumumab is also developed to target CD20; however, its binding site is closer to the cell membrane and with greater avidity than rituximab. This second-generation anti-CD20 monoclonal antibody is considered to be more effective, even in patients who did not benefit from rituximab. Unconjugated monoclonal antibody that targets CD22 is called epratuzumab. Treatment with epratuzumab was assessed in combination with conventional chemotherapy showing its feasibility in children with relapsed CD22-positive ALL. In several clinical trials, majority of patients achieved early responses [58, 59].

Alemtuzumab is a humanized monoclonal antibody against CD52. CD52 is expressed in about 50% of leukemia blasts, including B- and notably in T-ALL and AML. It was assessed in small groups of patients in combination with granulocyte-colony-stimulating factor (G-CSF) to boost antibody-dependent cell cytotoxicity mediated by neutrophils showing transient good responses [60]. One of the promising monoclonal antibodies that can be potentially used in AML is anti-CD33, lintuzumab [61, 62]. Clinical trials revealed high efficacy in the reduction of leukemic blasts, but remissions were only reported after effective cytoreduction, not in patients with high tumor burden [63].

To improve leukemic-targeted toxicity, we can also take one step further. If a target is known to internalize on binding, it is effective to use monoclonal antibodies conjugated to cytotoxic compounds, producing an additional mechanism for cytotoxicity. For example, CD22 is proven to be internalized on antibody binding. Inotuzumab ozogamicin is the antibody targeting CD22 linked to calicheamycin that showed improvement over chemotherapy including complete hematologic remission, longer progression-free, and overall survival [64, 65]. The analog that could have been potentially used in AML is gemtuzumab ozogamicin, targeting CD33. However, according to its toxicity and increased risk of veno-occlusive disease (VOD), it has been withdrawn in 2010. Another approach using antibody-dependent mechanisms of tumor cell lysis is using immunotoxins, which are recombinant anti-CD22 or anti-CD19 conjugated with Pseudomonas or Diphtheria endotoxins. Radioimmunoconjugates are monoclonal antibodies linked to radioactive isotopes that can be beneficial as the part of hematopoietic stem cell transplantation regimens, but they are non-preferential to be used in children.
Bispecific T-cell engagers (BiTEs) are designed to redirect and activate cytotoxic T cells precisely at the site of a tumor. The idea is to create antibody-based constructs that temporarily bridge T-cells and cancer cells. The most popular and widely investigated bispecific antibody, Blinatumomab, targets CD3 and CD19. Based on multiple clinical studies that have shown an achievement of durable complete remission and acceptable safety profile, the FDA granted accelerated approval for blinatumomab for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia in 2014 [66–68]. AML treatment requires using BiTEs that are compatible to antigens on myeloblasts. AMG 330 is designed to target CD33 and CD3. Clinical studies indicate that this approach is efficient in relapsed AML, especially when combined with blockade of the PD-1/PD-L1 [26].

2. Conclusions

In the era of discovering new approaches to improve survival in childhood hematological malignancies, immunotherapy has a strong position. Potential benefits that can be achieved by implementation of highly active targeted therapies in pediatric acute leukemia are numerous. Improved overall survival and event-free survival is the major advantage, but the possibility to reduce treatment-related toxicity is also extremely important for improving the convalescent’s quality of life. Treatment strategies are now actively investigated in multiple clinical trials, mostly in adults, but also in the pediatric population and the results are promising. However, they can be evaluated only in situations when there are no longer better treatment strategies present in refractory or relapsed leukemia, which means that their efficacy is being assessed in desperate settings with high blasts burden and more aggressive neoplastic cells mutated according to the previous treatment [69]. It would be important to evaluate the role of immunotherapy combined with frontline regimens, whether this approach optimizes the treatment efficacy. For example, remission induction is the phase of impaired T regs number and function, which indicates that it is potentially beneficial to combine the T regs depletion with cyto_reduction. What is more, it has been proven that the combination of different immunotherapeutic strategies has the synergistic effect. T regs depletion with CAR-T or bispecific antibodies straightens the efficacy of T cells cytotoxicity [26, 62].

There are still many challenges and difficulties to overcome to make the treatment of childhood acute leukemia more effective and safe. Apart from numerous studies that provide a better understanding of the biology and genetics of leukemia, the impact of immunological processes that influence the treatment response was underestimated for a couple of years. Significant breakthroughs achieved in immunotherapy that improved survival in patients with the most resistant disease triggered a renewed interest in this field of treatment. Immunotherapeutic strategies are being constantly improved using the advances of engineering techniques and a better understanding of immunological mechanisms that play a role in tumor surveillance. The assortment is impressive at the moment and is getting even wider, but it appears that in everyday clinical practice the opportunities are not adequately utilized.
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