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Immunotherapy for Acute Lymphoblastic Leukemia: Challenge and Promise

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Abstract

Acute Lymphoblastic Leukemia (ALL) comprises 80% and 20% of pediatric and adult leukemias, respectively. Treatment is successful in 80% children with ALL but the survival of relapsed cases is poor. In adults, the relapse rate is over 50% and the overall survival is 20-40%. Relapse, mainly due to multidrug resistance, is the major concern in acute leukemias. Chemotherapy intensification has largely improved the survival of children with ALL, but despite this modification, most of the relapsed cases will die. In addition, intensive regimes have high toxicity and several side effects and it might not feasible for the adult. Therefore, the development of novel therapeutic approaches is critical. One of these strategies is immunotherapy. In this paper, written in Iran, by reviewing 50 newest references (2005-2017) using Elsevier, OVID and Pubmed databases, different kind of immunotherapeutic approaches for ALL including antibody and cellular based therapies (such as naked antibodies, bi-specific T-cell engaging antibodies, antibody–drug conjugates, chimeric antigen receptor (CAR)-modified T cells, natural killer and DC-based and radioimmunotherapy) are briefly introduced. The promising trials are highlighted and the Abs based-immunotherapy-related challenges such as monoclonal Abs toxicities, immunogenicity, and the mechanisms of immunotherapy resistance are discussed. Finally, cellular based-immunotherapy-related problems such as cytokine release syndrome and other challenges are reviewed.

INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is the clonal disease. In this cancer, the immature cells (blasts) accumulate and the production of healthy hematopoietic cells decreases. According to involved lymphoid lineage, ALL is classified into two major subtypes: T- ALL or B- ALL [1]. ALL is the highest prevalent childhood leukemia (80%, the most common reason of cancer mortality in pediatrics) and accounts for approximately 20 % of Leukemias in adults [2, 3]. Despite many advances in ALL treatment, the occurrence of relapse is a leading therapeutic challenge, mostly due to chemoresistance [4, 5]. In adults, the relapse rate is higher than children (over 50% Vs 15-20%) [6]. Because of treatment-related toxicity, the intensification of chemotherapy isn't possible for some patients, especially older patients [7] and relapsed ALL recognized as an incurable disease in adult patients [8]. Therefore, the development of novel therapeutic strategies is a necessity. Immunotherapy is in the heart of more novel therapies for ALL patients [9, 10]. In this paper, the different types of ALL immunotherapeutic approaches are briefly introduced and the clinicians and researchers challenges described to date are reviewed.

Immunotherapy for ALL

Allogeneic stem cell transplantation (alloSCT) was the first immune-based therapy for patients with hematological malignancies. This approach is curative for a subset of patients [11] but all patients are not eligible for alloSCT and relapse still occurs in over 30 percent of transplanted patients [12, 13]. In addition, it often leads to significant short- and long-term toxicities [6]. So in an attempt to decrease relapse risk, minimize toxicities and improve overall survival alternative therapeutic were explored [6]. Tumor antigens include tumor- associated antigens (TAAs) and tumor-specific antigens (TSAs). As their names show TAAs are expressed on both malignant and normal cells while TSAs expression exclusively occur on malignant cells [14]. Table 1 shows TAAs of leukemic blasts. They are targeted by immunotherapy. In General, immunotherapy is divided into two major classes: Antibody-based and Cell-based therapeutics. In the following sections, different kinds of immunotherapy for ALL are described.

Table 1. Tumor- Associated Antigens of Leukemic Blasts

Lineage-specific surface antigen	ALL subtype	Function
CD 19: Type 1 the superfamily of immunoglobulin, a trans-membrane protein	B-precursor, Mature B-ALL	The regulation of B-cell fate and differentiation
CD 20: Calcium channel	B-precursor, Mature B-ALL	The influence on cell cycle progression and differentiation through signaling pathways that modulate pro-apoptotic proteins levels
CD 22: A member of SBIL* family of adhesion molecules	B-precursor, Mature B-ALL	The Regulation of B-cell activation and its interaction with T cell and APCs
CD 52: Peptide glycoprotein	B-precursor, T-precursor	The involvement in the CD4+ regulatory T cells induction

* Sialic-Acid-Binding Immunoglobulin-Like

Table 2. Bispecific Antibodies and Conjugated Abs

Lineage-specific Surface Antigen (Monoclonal Antibody)	The Type of Immunotherapy
CD 19	
Ofatumumab	Naked mAb
Blinatumomab	(BiTE)
SAR3419	Conjugated
CD 20	
Rituximab	Naked mAb
GA-101	Naked mAb
CD 22	
Inotuzumab	Naked mAb
Ozogamicin	Conjugated
BL22 (CAT-3888)	Conjugated
90Y-epratuzumab	Conjugated
CD 52	
Alemtuzumab	

Antibody-based Immunotherapy

Given the presence of TAAs, monoclonal antibodies (mAb) are being widely explored [9]. Some researchers mentioned that expression of target antigen by at least 20 percent of the leukemic cells is a requirement for mAb therapy but not all investigators use this criterion [15]. For several decades, the utility of some naked monoclonal antibodies in hematologic malignancies, including rituximab [18, 19], alemtuzumab [20], and epratuzumab [21] have demonstrated. The advantages of mAbs, rather the intensive chemotherapy and SCT include different and reversible toxicities and lack of multi drug resistance [22] but the modest success of naked-mAb monotherapy because of minimal and indirect cytotoxic effects or high leukemic burden in some cases (mostly refractory or relapsed, R/R, patients) at the testing time was one of its limitations [1]. A large number of strategies have been applied to improve the efficacy of mAbs. These consist of the stimulation or enhancement of immune effector mechanisms of host, mAb modification to enhance CDC (Complement-Dependent Cytotoxicity) and ADCC (Antibody-Dependent Cell-mediated Cytotoxicity), the development of mAbs with special binding properties (like bispecific antibodies) and the conjugation of mAbs with radionuclides or cytotoxic agents [1, 15]. Some examples of bispecific antibodies and conjugated Abs and their advantages and limitations are mentioned below, see also Table 2.

Bispecific (BiTE) antibodies are a new class of antibodies that contain two scFv (Single-Chain Variable Fragments). They simultaneously bind to $CD3^+$ T cells and a target antigen [23]. The first clinical use of BiTE was described in 1995 [24]. In 2014, Blinatumomab was approved by FDA as the first drug in BiTE class for the treatment of relapsed and/or refractory B-ALL [25]. The two scFv of Blinatumomab simultaneously target CD19 and CD3, connected by a short non-immunogenic linker [25]. BiTE antibodies at sub-picomolar concentration able to redirect target cell lysis through T-cells, in the presence of target cells they can activate T-cells to kill and allow to T-cells to lyse target cells in series [24]. This sequence of events results in a triggered activation of T-cells [9]. The promising efficacy along with a favorable safety profile was reported in the use of blinatumomab for R/R or MRD^+ (Minimal Residual Disease) B-cell precursor ALL patients [26] but in a significant number of patient relapse occur. It might be due to blinatumomab -resistance and an insufficient activity of this Ab in sanctuary sites (as a probable cause of extramedullary relapse especially in CNS) [26]. Moreover, in a case report the increase in PD-L1+ (Pro-

grammed Death-Ligand 1) ALL blasts was reported as a potential mechanism of immune escape in a blinatumomab –resistant patient [23]. Continuous infusion via central line and theoretical induction of peripheral tolerance because of T-reg cells recruitment are other shortcomings of Blinatumomab [27]. In addition, Design of BiTE is another issue and a balance of some features, including stability, target affinity, bioavailability, and efficacy must be considered. In the attempt to improve the bioavailability of Ab and mitigate the need for difficult continuous dosing, modifications of these antibodies platforms are being explored. The engineered antibodies in similar platforms are bivalent bifunctional dual affinity retargeting Ab (DARTs), tetravalent bifunctional tandem antibodies (TandAb), and trispecific antibodies. DARTs and TandAb have the longer half-life than BiTE because of their structure and the promising clinical results were reported but further studies are needed yet. For additional information, we refer readers to Connie Lee Batlevi et al paper [25].

Because of high radio-sensitivity of leukemic cells, the combination of therapeutic antibodies with a radionuclide could be a possible approach to improve the efficacy of them by combining the radiobiological cytotoxicity with immunologic cytotoxicity. For applying radio-conjugated Abs or radio-immunotherapy (RIT) different approaches have been assessed or are already developed in the treatment of acute leukemia in which α and β RIT target CD22, CD45 or other TAAs. For instance, monotherapy with Epratuzumab (anti CD22) has little anti-leukemic activity while its conjugation form with 90 Y showed improved activity [1]. In one B-ALL patient ($CD22^{+}Ph^{+}$) molecular remission has been reported after RIT with 90 Y-epratuzumab tetraxetan [28]. A phase 1 study of dose-escalation of 90 Y-radiolabeled-epratuzumab tetraxetan (90 Y-DOTA-hLL2) RIT was recently described for adults with R/R-ALL [29]. Some adverse events include pancytopenia and infection but at second RIT cycle in two of the three responders no toxicity were observed [1]. More investigations should be performed to weight benefits of RIT in therapeutic programs and provide additional experience regard this agent in pediatric ALL. Other forms of conjugated antibodies are toxic bound-Abs. Some examples are Inotuzumab ozogamicin (IO), SAR3419, BL22, and CAT-8015. IO is an anti-CD22 linked to calicheamicin, a potent anthracycline-like drug [22]. The Cytotoxic effect of IO is completely mediated by calicheamicin and CD22 expression is only required for its delivery to tumor cells [22]. It is considered as an encouraging potential therapy for R/R-ALL [30]. A Phase II trial on R/R ALL is being evaluated by applying SAR3419 , an anti-CD19 Ab conjugated to maytansinoid DM4; a powerful inhibitor of tubulin and the reversible dose-limiting corneal toxicity was reported [22]. The research on conjugated antibodies for patients with ALL and assessing their advantages and limitations are being continued. Overall, the use of Ab-based immunotherapy for ALL (particularly R/R-ALL) patients have encouraging results. However, for an optimal treatment approach, several details still must be defined including the required percentage of antigen expression, schedule, and timing, stage of disease, adequate dose, and optimal combinations of Abs with chemotherapy [7]. In addition, Abs often display intricate pharmacokinetic and pharmacodynamic features and because of the multiple mechanisms of their cytotoxicity and the complexity of their disposition nature, the determination of these parameters, will result in the improved development of mAbs [31]. Some considerations in light of Ab-based immunotherapy are listed below: The percentage of the leukemic cell expressing the target antigen, the cell surface density of it, the internalization rate, the efficacy of the toxins or radionuclide (in conjugated Abs), and the impact of the antibodies on the immune system influence on the efficacy of this type of therapy [32]. There are some challenges in Ab-based immunotherapy. They consist of expensive production of them, slow elimination from the blood and poor vascular permeability, possible immunogenicity of drug conjugate-Abs and remove from the system before binding to the target [16]. Several mechanisms of Ab-based immunotherapy resistance have been reported. Target cells may change their ligand expression [16]. It leads to the variation of target antigen expression (which might be intrinsic or acquired during therapy). This variation, the activation of alternative signaling pathways, and formation of anti-antibody are among resistance mechanisms [23]. For example, the significant change in CD20 expression, deficiency in redistribution of this antigen into domains of lipids raft or alteration of raft elements and a decrease in the mobilization of calcium are some potential mechanisms of resistance to rituximab. Changes in several signaling pathways, like NFκB, ERK1/2 are also described as the reasons of rituximab-resistant [31]. Host-related factors, inter-individual variability, including polymorphisms and pharmacokinetics should be also considered and further studies are needed yet to provide complete insight into this multifactorial phenomenon.

Cell-based Immunotherapy: Using Immune Cells as the Living Drugs

T cells are critical components of the immune system that fight to both pathogens and malignant cells. AlloSCT is one of the original forms of immunotherapy in cancer [33]. It is the earliest and most studied form of cell- based therapy in the leukemia treatment [34]. The only therapeutic approach for long-term disease free survival in relapsed patients is allo-HSCT if they are chemosensitive, have not received an allo-HSCT before, and have HLA-matched donor [34]. For many reasons, R/R-ALL patients might be transplant –ineligible [34]. In addition, there are the high levels of alloSCT - associated morbidity and mortality, including graft versus host disease (GvHD) [33] and conflicting results lead to controversy regarding the role of allo-HSCT for ALL patients [34]. These facts prompt the development of novel approaches to cell-based therapy in ALL. They entail genetically modified T Cells, Natural killer (NK) cell therapy and dendtritic (DC) cell therapy. The autologous T cells could be genetically modified to target TTAs. For this end, chimeric antigen receptors (CARs)-T cells could be produced. They are tumor-specific T cells with CAR. CARs are Chimeric proteins contain the fragments of both B and T cell receptor, thus the antibody recognition ability and the T cells capacity coming together for killing the target cells [35]. Various CAR-T-cell constructs exist and in order to improve their efficacy and persistence different generation were produced and are being explored [25]. This topic is beyond the scope of the current article and interested readers could study them elsewhere. To date, CAR-T-cell therapies have been most effective B-ALL patients. There are several clinical trials applying CD19-CAR

T cells. Several published results indicate that cellular therapy using autologous CD19-targeted CAR- T cells is a promising therapeutic strategy for B-cell malignancies [34]. The several papers have been reviewed CAR trials [25, 36-38]. The rapid generation of tumor-targeted T cells ex vivo and bypassing the barriers are some advantages of CAR-T-cells. Moreover, their generations addition to redirecting cytotoxicity, reprogram the function and longevity of T cell, therefore confer them supra physiological features, that exert immediate and persistent therapeutic effects [37]. The use CAR-T cell in comparison to conventional allo-HSCT has several benefits. In this approach, T cells rapidly are generated and the risk of GvHD is zero, due to utilizing autologous patient derived T cells. Moreover, its recognition of target antigen is not HLA-dependence thus it can be used to all HLA types. Strikingly, to augment anti-tumor efficacy of CARs we can genetically modify them to express proinflammatory cytokines or T-cell co-stimulatory molecules by insertion of additional genes [34]. The CAR- T cells are a patient-specific customized cellular therapy while BiTEs are conventional prepared drugs. According to Ruella and Gill, CART19, an anti CD 19 CAR-T cell, is more valuable than Blinatumomab, a BiET against CD 19. In spite of the broadly equal short-term anti-leukemic effect of the CAR-T cells and BiTE platforms, CART19 is preferred because it can best guarantee long-term anti-CD19 immunity [27]. However, there are two main CARs -associated safety concerns including the destruction of normal tissues and severe cytokine release syndrome (sCRS) in a subset of patients [37]. Another layer of complexity is the identification of an ideal dose of CAR-T cells is not easy because of high variation of cells expansion in vivo [25]. Further studies are crucial to determining the eligible patients and defining the optimal disease status for CAR- T-cell immunotherapy, to identify standardize approaches to the management of CRS, and determine the durability of remissions [6, 38]. The economics aspect of this therapeutic approach and its place in ALL treatment protocols must be considered.

Natural killer (NK) cells can kill a wide range of cancer cells [39]. Their activity is impaired in new-diagnosed leukemia patients. Allogeneic NK cells can control leukemia, they can induce remission in a subset of refractory AML (Acute Myeloid Leukaemia) patients, who did not respond to other treatments. These facts make NK cell an appealing candidate for cell-based immunotherapy [40]. However, the escape of leukemic blasts from NK –medited lysis, through induction of changes in NK cells via regulating TGF-β/ SMAD pathway, has been reported in pediatric B-ALL [41]. At another mechanism of escape, tumor cells express the cognate killer immunoglobulin-like receptors (KIR) ligands. Once they bind to KIRs on NK cells, as inhibitory receptors, the autologous NK cell-mediated immunity is limited. It seems that allogeneic NK cells are not the beneficial option in ALL [34]. To circumvent these problems different approaches are being explored to improve NK function including genetic modification, epigenetic therapies, immunomodulary blockade, and CAR-NK cells [34, 41]. For instance, Imai et al were generated CAR-NK cells through viral transduction of NK with chimeric anti-CD19-CD3ζ receptor. The modified cells exhibited increased lysis of NK cell-resistant ALL tumor cell lines [42]. Another group were described the considerable cytotoxicity of CAR- (antiCD19-BB-ζ)-NK cells in a mouse model of B-ALL, and offered a practical way to enhance the NK cells cytotoxicity against B-cell malignancies [43]. According to Cruz and Bollard, the combination of NK and T cells is an attractive strategy as a single immunotherapy [44] but many questions remained unanswered and further research are needed, particularly in ALL.

DISCUSSIONS

In summary, a number of antibody and cell-based immunotherapeutic strategies have been studies in patients with ALL and promising results have been reported. But due to many variations including patient age, the stage of diseases, targeted antigens, conjugated agents, and CAR constructs the head-to-head comparisons are not possible. In addition, further studies are required to overcome aforementioned challenges and define the exact role and place of each immunotherapeutic approach in the treatment of ALL. At last, two points must be emphasized. First, normal and malignant T cells share in the expression of most targetable antigens resulting in the rare immunotherapeutic options for T-ALL. However, the efficacy of CAR-T cells against CD5 in vitro and in vivo recently are investigated and therapeutic potential of them for T-ALL are mentioned [45]. Second, as mentioned before, TAAs are expressed both on malignant and normal hematopoietic cells thus, the cytotoxic effects of immunotherapy are less selective and resultant B or T-cell lymphopenia lead to immunotherapy-associated toxicities [7]. By using bioinformatics, highthroughput techniques of gene-expression profiling, flowcytometry and genomic data the attempts to identify novel antigenic targets with a favorable expression profile are being continued. The TSLPR, WT1, Survivin, PRAME and MAGE-A3 were proposed [10, 14]. CAR-T cells against TSLPR, an overexpressed surface protein in about 5–10% of patients with B-ALL, as the promising tools are reported [46]. Moreover, for effective prevention of relapse and improve long-term survival leukemic stem cell (LSC) must be targeted [47] and these quiescent and scarce cells beyond the bulk of leukemic blasts must be considered. It is reported that the drug conjugated- humanized anti-CD22 mAbs, inotuzumab ozogamicin (INO), not only deliver the drug to proliferating blasts but also able to target LSC [48]. The advantage of INO in adult patients was studied (INO-VATE Trial) [49] but finalized randomized trials specifically in childhood are not available [48] and further studies should be done.

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CONFLICTS OF INTEREST

There is no conflict of interest for the present study.

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AUTHOR'S CONTRIBUTIONS

M. Abedi and Z.Khosravi dehaghi contributed to collect data, their analysis and interpretation. M. Abedi wrote the manuscript.

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