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Review Article

Immunotherapy and Acute Lymphoblastic Leukemia

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Abstract

Acute lymphoblastic leukemia is a serious type of cancer that originates from the development and differentiation of the early version of lymphocytes in the bone marrow. With the advent of new technologies and discoveries, novel therapeutics was developed to treat these malignancies. Targeted immuno therapies are drugs that block the growth and spread of the cancer by interfering with specific molecules or pathways that are involved in carcinogenesis. It is a developing treatment alternative to chemotherapy and radiation. In this paper, we will discuss the current trends in various target therapies along with the different molecules involved in the proliferation of the disease.

Keywords: *Acute Lymphoblastic Leukemia; Immunotherapy; Immunosuppression; Kinase Inhibitors; Cytokines; Monoclonal Antibody; Interferons*

Abbreviations: ALL: Acute Lymphoblastic Leukemia; MABS: Monoclonal Antibodies; FDA: Food and Drug Administration; mTOR: Mammalian Target of Rapamycin Immunotherapy; IFN: Interferon; IL: Interleukin, NK: Natural Killer; ADC: Antibody Drug Conjugate

Introduction

Acute Lymphoblastic Leukemia (ALL) is a serious type of malignancies, which represents 0.1% of all the adult cancers and 25% of all the cancers diagnosed among children younger than 15 years [1,2]. According to the American Cancer Society, the age-standardized rate of incidence is eight cases per 100,000 in the age group of 1-4 years and one to two cases per 100,000 above the age of 55 years. The overall five-year survival rate is 68.8%. For children younger than 15 years, the survival rate is 91.7 and 92.6% for children younger than 5 years [3]. There is an annual increase of 1.4%, in the incidence worldwide [4]. In 2014, 6,020 new cases were diagnosed for ALL in the United States (U.S). Additionally, in the same year 1,440 cases of death were estimated [5]. The U.S., Italy and Switzerland have a high incidence rate, as compared to the rest of the world [6]. The cause for such higher incidence is unknown.

ALL includes different types of histopathological and genetic characteristics. There is a marginal predominance of males over females, [7] with the highest incidence, observed in between the ages of 1-4 years. The symptoms of ALL may include anemia, shortness of breath, fatigue, immunodeficiency and recurrent infection, bruising and unusual bleeding due to thrombocytopenia. The risk factors for ALL are unknown but it may be based on hereditary, genetic disorders like Down syndrome, Shwachman-Diamond Syndrome, Neurofibromatosis, Ataxia telangiectasia and Bloom syndrome, environmental exposures to household solvents, chemicals, pesticides and ionizing radiations [8].

Various cytogenetic modifications that occur in B-Cell precursor ALL (BCP-ALL) Hypodiploidy, Hyperdiploidy and Pseudoploidy occur in Burkitt's Type Acute Lymphmoblastic Leukemia (B-ALL) [9]. Translocations result in the generation of fused transcripts that have the capability to cause cancer [10].

T-cell ALLs (T-ALLs) represents 10-15% of ALL cases in children and 25% of the cases in adults [11]. The alterations in T-cells are associated with various genetic aberrations, leading to variations in the process like cell growth, proliferation, differentiation and apoptosis

[12]. NOTCH1 signaling and CDKN2A locus deletion in the 9p21 chromosome are the two most important factors that form the basis of leukemogenesis of T-ALL [12,13].

Immunotherapy

Humanized Monoclonal Antibodies (MABs)

Blinatumomab: It is indicated for the treatment of Philadelphia chromosome-negative, relapsed or refractory B-cell precursor acute lymphoblastic leukemia. Recombinant, single-chain, anti-CD19/anti-CD3 bispecific monoclonal antibody with potential immunostimulating and antineoplastic activities. Blinatumomab possesses two antigen-recognition sites, one for the CD3 complex marker, a group of T cell surface glycoproteins that complex with the T-cell receptor (TCR) and one for CD19 a B-cell specific marker. This bi-specific monoclonal antibody brings CD19-r B-cells and cytotoxic T lymphocytes (CTLs) and helper T lymphocytes (HTLs) together, which may result in the CTL and HTL-mediated cell death of CD19-expressing B-lymphocytes [14].

Side effects include the development of Cytokine release syndrome and toxicities of neurological nature. The adverse effects also include pyrexia, headache, peripheral edema, nausea, hypokalemia, tremor, rashes, constipation and immunodeficiency with recurrent infection.

The MABs that are currently under clinical trials in Phase I–III are as mentioned in Table-1 below:

Rituximab: It is a monoclonal antibody directed against CD20 antigen. It binds to this antigen, thus boosting the immune response.

Alemtuzumab: It is a monoclonal antibody directed against CD52 antigen. It binds to this antigen, thus boosting the immune response.

Inotuzumabozagamicin: It acts against CD22 antigen and internalizes the chemotherapeutic drug.

Epratuzumab: It is a monoclonal antibody directed against CD22 antigen. It binds to this antigen and mediates antibody-dependent cellular cytotoxicity (ADCC), thus boosting the immune response.

Anti-CD19 Immunotoxin: A mouse-derived anti-human CD19 monoclonal antibody linked to pokeweed (Phytolaccaamericana) antiviral protein (PAP) with anti-leukemic activity. The monoclonal antibody portion, specifically binds to the CD19 antigen, a cell surface molecule specific for B lymphocytes and follicular dendritic cells and over-expressed in B-lineage lymphocytic leukemia cells. Following internalization, PAP, a plant hemitoxin and a ribosome-inactivating proteinase cleaved from the immunoconjugate and released into the cytoplasm, where it enzymatically removes a single adenine base from a conserved, surface exposed loop sequence of rRNA leading to the inhibition of protein synthesis and cell growth, but not necessarily cell death.

Ipilimumab: A monoclonal antibody directed against cytotoxic T-lymphocyte-associated antigen-4 (CTLA4). An antigen that is expressed on activated T-cells and exhibits affinity for B7 co-stimulatory molecules. By binding CTLA4, ipilimumab enhances T-cell activation and blocks B7-1 and B7-2 T-cell co-stimulatory pathways.

MABs	Clinical Trial Identifier	Phase	Study Design	Target
Rituximab	NCT02043587	NCT02043587	Efficacy Study, Open Label	CD20 antigen
Alemtuzumab	NCT00773149	NCT00773149	Safety/Efficacy Study, Open Label	CD52 antigen
Inotuzumabozagamicin	NCT01363297	NCT01363297	Safety/Efficacy Study, Open Label	CD22 antigen
Epratuzumab	NCT00098839	NCT00098839	Open Label	CD22 antigen
Anti-CD19 Immunotoxin	NCT01408160	NCT01408160	Safety Study, Open Label	CD19 antigen
Ipilimumab	NCT01822509	NCT01822509	Safety Study, Open Label	CTLA4

Table1: *Non-FDA approved Monoclonal Antibodies [15–20].*

Tyrosine Kinase Inhibitors

The FDA approved TKIs are

Dasatinib: It acts as a TKI, specifically to the family of Src-protein tyrosine kinases. The SRC family usually, adheres to a number of receptors, available on the surface of the cell, resulting in a cascade of signaling pathways. It is used in the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL), with resistance or intolerance to other therapies [21].

Side effects may include myelosuppression and bleeding Events, severe thrombocytopenia, neutropenia, primary immunodeficiency and anaemia, fluid retention, QT Prolongation, cardiac dysfunction, pulmonary arterial hypertension, embryo-fetal toxicity.The adverse effects may also include myelosupression, edema, diarrhea, headache, skin rash, fatigue, nausea and hemorrhage.

Imatinib: It is used in treatment of children with (Ph+ ALL), in combination with chemotherapy. It adheres to TK and prevents ATP phosphorylation and further growth receptor activation, which inhibits the cascade of signaling pathways, resulting in reduced cell proliferation and tumor cell death. It is also indicated as a single agent for the treatment of adult patients, with relapsed or refractory Ph+ ALL [22].

Side effects may include edema and severe fluid retention, cytopenias particularly anaemia, neutropenia and thrombocytopenia, severe congestive heart failure and left ventricular dysfunction, severe hepatotoxicity, gastrointestinal perforations, bullous dermatologic reactions like erythema multiform and Stevens-Johnson syndrome, hypothyroidism, embryonal fetal toxicity, growth retardation in children and pre-adolescents and tumor lysis syndrome. Other adverse effects may include nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhoea, rash, fatigue and abdominal pain.

Ponatinib: It is indicated for T315I-positive Ph+ ALL patients. This agent also inhibits other TKs, including those associated with vascular endothelial growth factor receptors (VEGFRs) and fibroblast growth factor receptors (FGFRs) in addition, it inhibits the tyrosine kinase receptor TIE2 and FMS-related tyrosine kinase receptor-3 (FLT3). RTK inhibition by ponatinib hydrochloride may result in the inhibition of cellular proliferation and angiogenesis and may induce cell death. Bcr-Abl is a fusion tyrosine kinase, encoded by the Philadelphia chromosome [23].

It is also indicated as a therapy for the treatment of adult patients of Ph+ ALL, to whom no other TKI therapy is indicated.

Major adverse effects may include Cardiovascular, cerebrovascular and peripheral vascular thrombosis, including fatal myocardial infarction and stroke, hepatotoxicity, liver failure and death. In addition to Congestive heart failure, hypertension, pancreatitis, haemorrhage, fluid retention, cardiac arrhythmia, myelosuppression, tumour-lysis syndrome, compromised wound healing and gastrointestinal perforation, and embryo-fetal toxicity. Other adverse effects may include hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea and pyrexia. Hematologic adverse reactions include thrombocytopenia, anaemia, neutropenia, lymphopenia and leucopenia.

The other kinase inhibitors that are under clinical trials for ALL include

Nilotinib: An orally bioavailable aminopyrimidine-derivative Bcr-AblTKI with antineoplastic activity. Designed to overcome imatinib resistance, nilotinib binds to and stabilizes the inactive conformation of the kinase domain of the Abl protein of the Bcr-Abl fusion protein, resulting in the inhibition of the Bcr-Abl-mediated proliferation of Ph+ chronic myeloid leukemia (CML) cells. This agent also inhibits the RTKs platelet derived growth factor receptor (PDGF-R) and c-kit, a RTK mutated and constitutively activated in most gastrointestinal stromal tumors (GISTs). With a binding mode that is energetically more favorable than that of imatinib, nilotinib has been shown to have an approximately 20-fold increased potency in kinase and proliferation assays compared to imatinib.

In a phase-II clinical trial study conducted by Deremer., *et al*, the pharmacology, pharmacokinetics and pharmacodynamic studies of nilotinib were done on patients with CML, Ph+ ALL and GISTs. In 32 out of 33 cases of Bcr-Abl mutations that were resistant to imatinib, nilotinib was found to be active [24]. However, the cases were not same for T3151 mutations. T_{max} and $t^{1/2}$ was found to be three hours and 17 hours respectively. Nilotinib may lead to prolonged QT interval and hence to sudden death [24].

PLX3397: A capsule formulation containing a small-molecule RTK inhibitor of KIT, CSF1R and FLT3 with potential antineoplastic activity. Multitargeted TKI, PLX3397 binds to and inhibits phosphorylation of stem cell factor receptor (KIT), colony-stimulating factor-1 receptor (CSF1R) and FLT3, which may result in the inhibition of tumor cell proliferation and down-modulation of macrophages, osteoclasts and mast cells involved in the osteolytic metastatic disease. FLT3, CSF1R and FLT3 are over expressed or mutated in many cancer cell types and play major roles in tumor cell proliferation and metastasis. Adverse effects may be severe [25].

Adoptive T-cell Therapy

There is no adoptive therapy that is currently approved by FDA for ALL. However, many such therapies are under clinical trials in phase I–III.

Twenty-seven out of 29 patients with an advanced blood cancer who received an experimental, "living" immunotherapy as part of a clinical trial experienced sustained remissions, according to preliminary results of the ongoing study at Fred Hutchinson Cancer Research Center. Some of the patients in the trial, which began in 2013, were originally not expected to survive for more than a few months because their disease had previously relapsed or was resistant to other treatments, said Dr.Stanley Riddell, an immunotherapy researcher and oncologist Fred Hutch.

Riddell, who has studied how to empower the immune system to effectively treat human disease for more than 25 years, said that progress now being made, underscored by these latest results, is finally making immunotherapy "a pillar of cancer therapy." The trial is designed to test the safety of the latest iteration of an experimental immunotherapy in which a patient's own T cells are reprogrammed to eliminate his or her cancer. The reprogramming involves genetically engineering the T cells with synthetic molecules called chimeric antigen receptors or CARs that enable them to target and destroy tumor cells bearing a particular target. Trial participants include patients with acute lymphoblastic leukemia, non-Hodgkin lymphoma and chronic lymphocytic leukemia. Because T cells can continue to multiply once infused into patients, the therapy does not have to be administered repeatedly, as is the case with chemotherapies that are eventually broken down by and eliminated from the body. And by introducing the CARs into two specific subsets of T cells - an approach pioneered at Fred Hutch - the researchers have achieved more potent and longer-lasting immune responses against tumours [26].

Autologous Natural Killer Cells

These are cytotoxic Natural Killer (NK) cells and have anticancer properties. They target Tumor Associated Antigens (TAAs) that are found to be upregulated in few cancer cells[27].

Other types of adoptive therapy include the use of genetically modified T-cells that can express Chimeric Antigen Receptors (CARs). The aim is to target CD19 antigen, which is observed in all the B-ALL cases. CARs are the modified constructs of the receptor that consist of a domain, which is specific for the target recognition. This domain is conjugated with a component that exists intracellularly and triggers a cascade of signals in the immune effector cell. The first case of B-ALL, treated with CAR T-cells, has been done by Memorial Sloan Kettering Cancer Centre. On second remission, this patient was given hybrid T-cells that would express CD-3 targeted CAR. After administration of cyclophosphamide, γ-interferon was introduced that led to serious B-cell aplasia [28]. After eight weeks, allo-HSCT was achieved. Five more ALL patients were introduced to the group [29]. Complete remission was observed in all five of them, without any Minimal Residual Disease (MRD). Allo-HSCT was done in another study, where four patients, out of which, three had remissions, while one of them died of post-transplant complications. One patient that did not undergo allo-HSCT showed signs of remission after 13 weeks of CAR treatment [30].

mTOR Inhibitors

There is no mTOR inhibitor that is currently approved by FDA for ALL. However, the below mentioned mTOR inhibitors are under clinical trials.

Sirolimus: It adheres to the FK Binding Protein-12 (FKBP-12) to generate an immunosuppressive complex that inhibits the key regulatory kinase mammalian Target of Rapamycin (mTOR), a key regulatory kinase [31].

Everolimus: It is a macrocyclic derivative of sirolimus. It acts by adhering to the immunophilin, FKBP-12 and develops a complex that is immunosuppressive in nature. This complex adheres and inhibits mTOR, which further inhibits activation and proliferation of T-lymphocytes and production of antibodies in childhood ALL [32].

MTOR Inhibitors	Clinical Trial Identifier Number	Phase	Study Design	Target
Sirolimus	NCT01658007	Phase-I	Safety Study, Open Label	FKBP-12
Everolimus	NCT01523977	Phase-I	Safety/Efficacy Study, Open Label	FKBP-12

***Table 2**: Non-FDA approved mTOR Inhibitors [31,32].*

Proteasome Inhibitors

There is no proteasome inhibitor that is currently approved by FDA for ALL. However, the below mentioned proteasome inhibitors are under clinical trials, as in the Table 2 below:

Bortezomib: It reversibly inhibits the 26S proteasome, a large protease complex that degrades ubiquinated proteins, by blocking the targeted proteolysis normally performed by the proteasome. Bortezomib disrupts various cell signaling pathways leading to cell cycle arrest, apoptosis and inhibition of angiogenesis. Specifically, the agent inhibits Nuclear Factor (NF) - kappa B, a protein that is constitutively activated in some cancers, thereby interfering with NF-kappa B-mediated cell survival, tumor growth and angiogenesis. *In vivo*, bortezomib delays tumor growth and enhances the cytotoxic effects of radiation and chemotherapy.

Bortezomib	NCT02112916	Phase-III	Study Design	Target
Bortezomib	NCT02112916	Phase-III	Efficacy Study, Open Label	26S proteasome

***Table 3:** Non-FDA approved Proteasome Inhibitors [33].*

Conclusion

Various monoclonal antibodies and TKIs are FDA approved immunotherapeutic agents, available for ALL and a number of clinical trials are currently going on for various classes like MABs, adoptive therapy, vaccines and TKIs. Stem cell transplantation is another treatment therapy for ALL however, no data is available yet. The complete perspective of immunotherapy treatment has not been realized and/or utilized. Proper pre-clinical and clinical designs are the important pillars in understanding the future of immunotherapy in treating ALL patients.

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