Immunotherapy in Childhood Acute Lymphoblastic Leukemia

Gazmend Temaj
University for Business and Technology - UBT, gazmend.temaj@ubt-uni.net

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Gazmend Temaj[1], Kumrije Sopi-Xharra[2], Shefki Xharra[2]

[1]College UBT, Medical Faculty, Lagjja Kalabira 56, Prishtinë, 10000 Kosova
[2] Regional Hospital Prizren, Sheh Emini nn, Prizren, 20000 Kosovo
{gazmend.temaj@ubt-uni.net, kumrijensopi@gmail.com, saxharra@gmail.com

Abstract. Acute lymphoblastic leukemia (ALL) is known as a heterogeneous disease. The progress is possible to make in understanding of biological mechanism who play pivotal role in the development of therapies. Here I will try to summarize the current and future possibilities of management of adult and children ALL. Many inhibitors are used to inhibit tyrosine kinase, chimeric antigen receptor and gene therapy for cure of ALL. The FDA has approved a number of drugs for treatment of children who are sick from ALL. Currently, is known that long term of survival is achieved in more than 50% of patients with B-ALL, 50-60% T-ALL, and 80% mature ALL. In era of precision medicine, the future is based in using of less cytotoxic and based and more target agents.

Keywords: acute lymphoblastic leukemia, clinical features, chemotherapy, immunotherapy

1 Introduction

It is known that leukemia is the most frequently malignancy disorders, account for 30% of childhood cancer diagnosis [1]. More than three-quarters of patients who are attack from ALL (acute lymphoblastic leukemia), are diagnosed with B-ALL, and others are diagnosed with other subtypes such T-ALL, ALL Ph+, ALL Ph-. The treatment of childhood with ALL last decade is improved, and 90% of children survive from initiate phase of diagnosis [2]. Although improve of therapy, the burden of therapy for children who are treated is essential, with short and long term toxicities, for some not so well , such as infants, adolescences, and adults [3, 4].

Novel approach are needed to improve results for poor-risk subsets and to potentially relapse components of cytotoxic chemotherapy. Immunotherapy play important role, particularly for children who are attacked from ALL.

1.1 Clinical features of ALL

Childhood ALL is consider as a sporadic diseases, with <5% of cases due to an underlying genetic predisposition [5, 6]. The risk stratification is import to maximizing cure of children with ALL, minimizing side effect. Clinical feature, blast genetics, and early treatment are shown to play pivotal role for prognostic variables used for risk stratification. Minimal residual disease (MRD), measured by flow cytometry and PCR is the most significant prognostic factor [7, 8].

In contrast, children who have new diagnosis, the prognosis for those who relapsed is poor, and is shown to be characterized with resistance on therapeutic agents [9-11].

1.2 Immunotherapy

For treatment of ALL, the novel targeted approaches are urgently needed. Several immunotherapeutic agents have used for treatment of ALL patients and care for relapsed/refractory disease and new investigated of regime treatment.

1.3 Blinatumomab

Blinatumomab is a first – in class bispecific T-cell engager (BiTE). Bilantumomab is known to consist of two different single chain Fv fragments joined by a glycine-serine linker. During the phase I efficacy of blinatumomab is shown to be very poor in non-Hodgkin lymphomas patients [12]. During the phase II blinatumomab (15ug/m2day for 4 weeks) demonstrate in adult relapse or persistence of MRD (minimal residue disease) in B-ALL response in 16 of 20 (80%) evaluable patients, and relapse-free survival of 61% [13, 14]. A phase III a multi-institutional study in 405 adult patients with ALL, 271 patients received blinatumomab; it is shown better remission for patients treated with blinatumomab with or without hematological recovery, and better median survival [15]. To confirm the effects of blinatumomab during the phase II which is given B-ALL with positive MRD [16], from 113 patients, 88 (78%) experienced a complete MRD response after first cycle of treatment [16]. Blinatumomab was tested also in treatment of patients with Ph- positive ALL, when is shown that inhibition of tyrosine kinase inhibition was not successful [17]. The unique significance toxicities in the patients treated with blinatumomab are CRS (cytokine release factor) and neurological events [15, 18]. Symptoms of CRS include pyrexia, headache, nausea, fatigue, and hypotension; the neurological symptoms include headache, malaise, confusion, disorientation, encephalopathy, and convulsions [19]. The loss of expression of CD19, targeted by blinatumomab, is the major mechanism of resistance during treatment with this drug. This drug have possibilities to activate T-cell which are called regulatory cells. The T-cell lead IL-10 production, suppressing effector T-cell proliferation and in the same way reducing the toxicity activity of CD8 T cells [20].

1.4 Inotuzumab Ozogamicin

Inotuzumab ozogamicin is CD22 humanized monoclonal antibodies who have the possibilities to conjugate with calicheamicin [21]. After inotuzumab bind CD22, the complex slowly is dissolved by lysosome [22]. Calicheamicin has shown to bind DNA in the minor groove and cause double-break [23]. In phase I/II studies this

compound has given 1.2 mg/m2 to 1.8 mg/m2 per cycle for adult patient attacked by ALL, the overall response was 57% to 68%. In phase III of the study the remission has completely significant higher with patients treated with inotuzumab compared with patients treated with chemotherapy [24] (Figure 1).

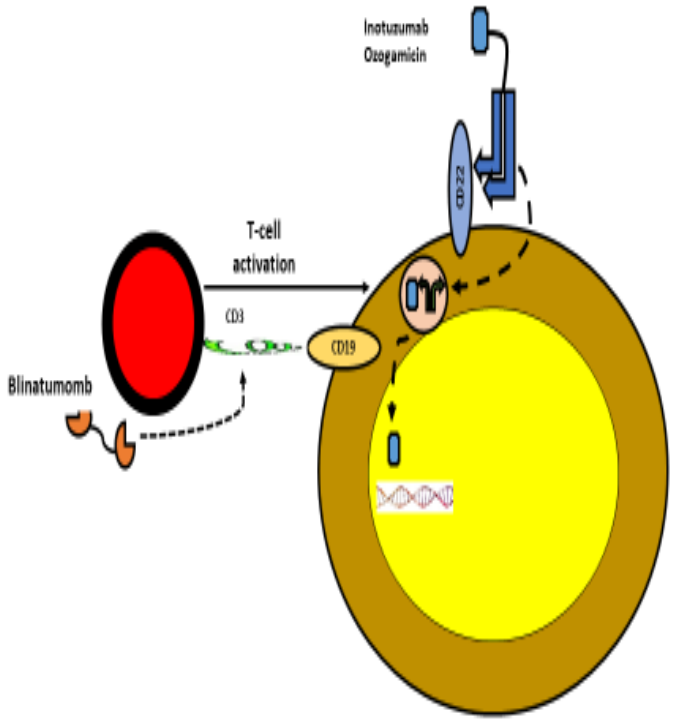

Fig. 1. The therapeutic targets in acute lymphoblastic leukemia

2 Conclusion

Immunotherapy has improve dramatically relapse/refractory of ALL patients, and a number of agents are now integrated into therapy. Based on experience, a variety of treatment modification, such as integration of therapies, dual target antigens designed

to overcome the immunosuppressive microenvironment, and design of third or four generation of candidate drugs for better ALL therapy.

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