



Editorial

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Newly Approved Immunotherapies for Adult Precursor B-acute Lymphoblastic Leukemia

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Submission: September 12, 2017; **Published:** September 14, 2017***Correspondence Address:** Nahla AM Hamed, Professor of Hematology, Faculty of Medicine, Alexandria University, Egypt, Email: drhamedn@hotmail.com**Abstract**

Most adults with B-cell precursor ALL will relapse and will die from complications of resistant disease or associated treatment. A major goal in B-cell precursor ALL is to induce remission of sufficient duration to prepare for stem-cell transplantation. The US FDA has recently approved three immunotherapies for this disease. CAR-T therapy, for the treatment of patients up to 25 years of age with B cell precursor ALL that is refractory or in second or later relapse, INO for the treatment of adults with R/R CD22 positive precursor B ALL and blinatumomab for treatment of precursor B ALL in adult and pediatric population.

Abbreviations: Allo-HSCT: Allogeneic Hematopoietic Stem Cell Transplantation; CAR-T: chimeric antigen receptor T cell; Ph: Philadelphia Chromosome; INO: Inotuzumab ozogamicin; CRS: Cytokine Release Syndrome; MRD: Minimal Residual Disease; AE: Adverse Events; ALL: Acute Lymphoblastic Leukemia; VOD/SOS: Veno-Occlusive Liver Disease/Sinusoidal Obstruction Syndrome; R/R: Relapsed or Refractory; CR: Complete Remission; OS: Overall Survival

Introduction

Precursor B-ALL is characterized by proliferation of lymphoblasts arrested at an early stage of B-cell maturation [1]. Most adults with B-cell precursor ALL will relapse and will die from complications of resistant disease or associated treatment. The remission rates among R/R adults ALL are 18 to 44% with standard salvage chemotherapy, but the duration of remission is typically short. The median OS among R/R ALL patients range from 2 to 6 months, and 3-to-5-year survival rates are less than 10% [2].

More effective treatment is needed to induce remission of sufficient duration to prepare for stem-cell transplantation in relapsed and refractory adults ALL [2]. Several surface antigens (CD-19, CD20, and CD22) are expressed on B-cell precursor ALL blasts, which allows for the use of targeted therapies. CD-19 is expressed on the surface of more than 90% of B-cell precursor ALL blasts. CD20 is expressed on B-cell precursor leukemic cells in up to 50% of patients [2]. CD22 is expressed in more than 90% of B-cell ALL patients [2]. Four types of immunotherapies have been developed to date, including naked monoclonal antibodies (such as rituximab), conjugated monoclonal antibodies (such as inotuzumab ozogamicin), bispecific T cell engager (BiTE) (such as blinatumomab), and CAR-T cell therapy [3].

Rituximab

Rituximab is an unconjugated CD20 monoclonal antibody that had minimal efficacy in the treatment of B-cell precursor ALL. Addition of rituximab to intensive chemotherapy was associated with longer survival in CD20-positive B-cell precursor ALL than was intensive chemotherapy alone [2].

Inotuzumab ozogamicin (INO)

INO is an antibody-drug conjugate that consists of a derivative of calicheamicin (a potent DNA binding cytotoxic agent) attached to an engineered humanized monoclonal immunoglobulin G4 antibody targeting CD22 [4]. CD22 is one of the most commonly expressed antigens on mature and immature B cells [4], and on most B-cell malignancies [5]. CD22 is not expressed on pluripotent hematopoietic stem cells [4]. Thus, it becomes an attractive target for drug delivery [5]. CD22 is a member of a homologous family of sialic-acid-binding immunoglobulin-like lectins (siglecs), which comprise a group of receptors that are restrictedly expressed in immune cells. Siglecs are endocytic receptors where cytotoxic agents conjugated to an antibody can bind and effectively carried into the cell without shedding into the extracellular environment [4].

The US FDA has approved INO for the treatment of adults with R/R CD22 positive precursor B ALL [6]. The use of inotuzumab in adult patients with Ph chromosome positive ALL, R/R CD22 positive B cell precursor ALL is restricted to those who failed treatment with at least one line tyrosine kinase inhibitor [6]. Treatment with INO in R/R ALL patients, resulted in higher rates of CR (81%) and higher rates of negative MRD (78%) than the rates seen with chemotherapy (29% and 28% respectively) [2,6]. HSCT was also more common with inotuzumab treatment (48% vs. 22%) [6]. OS was not significantly longer with inotuzumab (7.7 months) than with chemotherapy (6.2 months) [2,6]. The recommended duration of treatment for patients proceeding to HSCT is 2 cycles and up to a maximum of six cycles may be administered for patients not proceeding to HSCT. If no response occurs after 3 cycles, treatment with INO should be discontinued [5].

Treatment-Related AEs

In INO-VATE ALL, the incidence of Grade ≥ 3 treatment-related AEs was $\geq 15\%$. The most commonly reported AE in INO recipients vs. standard therapy were neutropenia (34% vs. 36%), thrombocytopenia (20% vs. 47%) and leucopenia (15% vs. 26%). Platelet transfusions were administered in (64% vs. 95%). Serious AEs occurred in (48% vs. 46%). Febrile neutropenia was the most commonly reported serious adverse event in both treatment groups (12 vs. 18%) [5]. VOD/SOS occurred in (13% vs. 1%) and was reported up to two years after randomization [7]. Inotuzumab includes a boxed warning of the risk of severe hepatotoxicity including SOS or VOD [6]. Increased hepatotoxicity especially after follow up HSCT occurs more than standard care. Of the INO recipients who underwent HSCT after the trial, VOD occurred in 22% after transplantation; (vs. 3% of the standard therapy recipients), five cases were fatal [7].

Dose interruption, dose reduction or permanent INO discontinuation may be required to manage adverse events [5]. Treatment should be paused or reduced if hepatotoxicity occurs and ceased if VOD occurs [6]. INO is contraindicated in patients with prior confirmed severe or serious ongoing VOD/SOS, or with serious ongoing liver disease [5]. Treatment-related deaths occurred in four INO recipients and two standard therapy recipients during treatment in INO-VATE ALL [5]. Pregnant or breastfeeding should not take the drug as it causes harm to newborn or fetus [6].

Therapeutic Trials

Promising results with inotuzumab combined with attenuated chemotherapy have been shown in two ongoing phase 2 studies in adults and elderly patients with R/R or with newly diagnosed precursor B-ALL [8].

CAR-T Therapy

A form of immunotherapy that utilizes the patient's own genetically modified T cells to target the CD19 on the surface

of leukemic cells. Once modified the cells are injected back into the patients [9]. Tisagenlecleucel is the first CAR-T therapy, approved by US FDA for the treatment of patients up to 25 years of age with B cell precursor ALL that is refractory or in second or later relapse [10]. Treatment with CAR-T cells that target CD19 was associated with complete response rates of 70 to 90% and durable remissions involving patients who had MRD or overt relapse in single-center trials [2]. Complete response or complete response with incomplete blood count recovery was achieved within 3 months of treatment in 83% of patients. There was also no evidence of MRD - a marker prognostic for potential relapse [9].

The most frequently reported grade 3 or 4 AE is CRS and neurologic events. Other commonly occurring AEs include serious infections, hypotension, fever, hypoxia and acute kidney injury [9]. CD19 CAR therapies eliminate normal mature and precursor B cells. Chronic B-cell aplasia and resultant hypogammaglobulinemia is an expected on-target toxicity of successful CD19-directed CAR-T therapy [11].

Relapse after CAR-T therapy remains a challenge. Two modes of disease recurrence have been seen: CD19 positive and CD19 negative. ALL relapse that retains surface CD19 expression results from rapid disappearance of CAR-modified T cells or decreased function of those T cells. Prolonging T-cell persistence by optimizing CAR designs, manufacturing technologies, or T-cell subset ratios may prevent some of these relapses. CD19-negative relapse is caused by escape variants. Single-target therapy may select for and lead to escape variants. Escape variants may be prevented by combination or tandem CARs, which join 2 antigen-recognition moieties, but further studies are needed. CAR-T cells targeting the B-cell antigen CD22 can be used for treating CD19-negative relapse and could be combined with a CD19-directed CAR in the future [11].

Blinatumomab

Blinatumomab is a bispecific T-cell engager antibody construct that binds simultaneously to CD3-positive cytotoxic T cells and to CD19-positive B cells. This allows the patient's endogenous T cells to recognize and eliminate CD19-positive ALL blasts [2]. The FDA recently approved blinatumomab for treatment of precursor B ALL in adult and pediatric population [6]. Blinatumomab lacks FDA approval for patients with Ph-positive ALL [12].

Blinatumomab resulted in significantly higher rates of hematologic remission and longer survival than chemotherapy. In a pivotal, multicenter, single group, phase 2 trial of blinatumomab in Ph-negative R/R adults ALL, the rate of CR with complete or partial hematologic recovery was 43%, and the median OS was 6.1 months. Single-group trials have shown the efficacy and safety of blinatumomab in the treatment of heavily pretreated Ph-negative R/R B-cell precursor ALL [2]. The facts that these patients are previously exposed to myelosuppressive

and immunosuppressive treatments, and the dependence of blinatumomab activity on functioning T cells, provides encouragement that additional immune activation strategies may further enhance blinatumomab response and made it durable [2].

The most common adverse effects are pyrexia (62%), headache (36%), peripheral edema (25%), febrile neutropenia (25%), nausea (25%), hypokalemia (23%) and constipation (20%). Serious adverse reactions occurred in 65% of patients in clinical studies and include pneumonia, sepsis, device-related infection, tremor, encephalopathy, confusion, and staphylococcal bacteremia. Tumor lysis syndrome is also possible [12]. CRS is important for blinatumomab pharmacodynamic response. It occurs as a result of the immune stimulation induced by blinatumomab, but is responsible for many adverse effects, including pyrexia, hepatotoxicity, disseminated intravascular coagulation, hypotension and capillary leak syndrome. Headache, nausea and weakness are possible. Dose interruptions and permanent therapy discontinuation has to be considered in the case of serious adverse effects [12].

Therapeutic Trials

- i. A global phase 2 study with blinatumomab in MRD positive ALL patients has shown 80% rate of molecular response and improved OS, independent of the subsequent HSCT realization [8].
- ii. Another phase 2 study with blinatumomab in R/R Ph+ ALL has shown a CR rate of 36%, independent of the ABL mutation status [8].
- iii. A phase 2 single-arm multicenter clinical trial of blinatumomab in Ph-positive B-precursor ALL patients, R/R to at least one second-generation TKI (dasatinib, nilotinib, bosutinib, ponatinib) or intolerant to second-generation TKIs and intolerant or refractory to imatinib is under study [12].
- iv. Two phase 3 studies with INO and blinatumomab, respectively in R/R precursor B-ALL patients, have demonstrated significant improvement in the CR rate and the OS compared with standard of care chemotherapy. These therapies should be currently considered as a bridge to HSCT in these patients [8].
- v. Blinatumomab and inotuzumab integrated with chemotherapy schedule especially during consolidation are

currently being investigated in newly diagnosed patients with precursor B-ALL [8].

vi. Combinations of targeted therapies have not been investigated [2].

Conclusion

INO and blinatumomab should be currently considered as a bridge to HSCT in patients with precursor B-ALL.

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