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• پنجشنبه 30 آذر 1399

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Immunotherapy

in

ALL

INTRODUCTION:

- The 5-year survival rate for children and adolescents with acute lymphoblastic leukemia (ALL) has improved to more than 90% in high-income countries.

INTRODUCTION(2):

- The approval of antibody-based therapy (with **blinatumomab** in 2014 and **inotuzumab** ozogamicin in 2017) and T cell-based therapy (with **tisagenlecleucel** in 2017) by FDA has significantly improved the response rate and outcomes in patients with relapsed/refractory B-ALL.

INTRODUCTION(3):

- The last decade has seen significant advances in *targeted therapy* with immunotherapy and molecular therapeutics, as well as *advances in risk stratification* for therapy based on somatic and germline genetic analysis and monitoring of minimal residual disease.

INTRODUCTION(4):

- Incorporating effective immunotherapy into ALL therapy would enable the intensity of conventional chemotherapy to be decreased and thereby reduce associated toxicity, leading to further improvement in survival and quality of life for patients with ALL

Blinatumomab

Mechanisms of action

- T cells play a critical role in controlling tumor growth. Because T cells lack Fcγ receptors, conventional antibodies cannot recruit T cells after binding to the target leukemia cells.

Blinatumomab

Mechanisms of action

- Therefore, an alternative approach has been developed to enhance the high cytotoxic potential of T cells by using bispecific T cell–engaging (BiTE) antibodies, Blinatumomab consists of 2 different single-chain Fv fragments joined by a glycine–serine linker.

Blinatumomab

Mechanisms of action

- One specificity is directed against the CD3 antigen of human T cells, which activates the cytotoxicity of T cells, and the other site binds the pan-B-cell marker CD19, which is uniformly expressed on the vast majority of B-ALL cells.

Blinatumomab

Mechanisms of action

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Clinical studies on blinatumomab in adults with refractory or relapsed B-ALL

- Subsequently, a phase II study of blinatumomab was performed in adults with refractory/relapsed Philadelphia chromosome (Ph)–negative B-ALL with $\geq 10\%$ blasts in the bone marrow .
- Because of the high disease burden, blinatumomab was given in stepwise increments (9 $\mu\text{g/day}$ for 1 week followed by 28 $\mu\text{g/day}$ for 3 weeks for cycle 1) to prevent cytokine release syndrome (CRS).

Clinical studies on blinatumomab in adults with refractory or relapsed B-ALL

- Of the 189 patients enrolled in the study, 81 (43%) experienced complete remission with or without hematologic recovery, and 32 (40%) of these 81 patients subsequently received an HSCT.

Clinical studies on blinatumomab in adults with refractory or relapsed B-ALL

- Blinatumomab was also effective in patients who had previously received an HSCT, with a response rate of 45% (29 of 64), which was comparable to the rate in those patients who had not previously received an HSCT (43%; 54 of 125)

Clinical studies on blinatumomab in adults with refractory or relapsed B-ALL

The U.S. Food and Drug Administration (FDA) granted accelerated approval of blinatumomab for patients with Ph-negative relapsed or refractory B-ALL in December 2014 .

- In a multi-institutional randomized phase III trial in 405 adults with refractory/relapsed B-ALL with >5% bone marrow blasts (the TOWER study), patients received either blinatumomab (271 patients) or standard-of-care chemotherapy (134 patients) at a 2:1 ratio .

Clinical studies on blinatumomab in adults with refractory or relapsed B-ALL

Patients treated with blinatumomab had a better complete remission rate with or without hematologic recovery (44% vs. 25%, $P < 0.001$), better event-free survival (31% vs. 12% at 6 months, $P < 0.001$), and better median overall survival (7.7 months vs. 4.0 months, $P = 0.01$) when compared to those treated on the chemotherapy arm.

Clinical studies on blinatumomab in adults with refractory or relapsed B-ALL

- To confirm the effects of blinatumomab in an earlier phase II study , blinatumomab was given to adults with B-ALL with positive MRD ($\geq 1 \times 10^{-3}$).

Clinical studies on blinatumomab in adults with refractory or relapsed B-ALL

- Of the 113 evaluable patients who received blinatumomab, 88 (78%) experienced a complete MRD response after 1 cycle of treatment. The median overall survival was 36.5 months, and the 18-month relapse-free survival was 54%, which was better than the prespecified boundary of 28%. Of the 74 patients who underwent a subsequent HSCT, 36 (49%) remained in remission.

Clinical studies on blinatumomab in adults with refractory or relapsed B-ALL

- However, of the 36 patients who did not receive a subsequent HSCT or chemotherapy after blinatumomab treatment, 9 (25%) also remained in complete remission with a median follow-up of 24.0 months. The authors of the study suggested that this finding might be of therapeutic relevance for less fit and elderly patients.

Clinical studies on blinatumomab in adults with refractory or relapsed B-ALL

- This study included 41 patients (35% of the total) who were in second or third remission. Although the MRD response was similar in these patients and in those in first remission, relapse-free survival was, not surprisingly, worse among the former patients (11.0 months vs. 24.6 months, $P = 0.004$).

Clinical studies on blinatumomab in adults with refractory or relapsed B-ALL

- Hence, earlier administration of blinatumomab during the disease course should be considered for patients with persistent MRD .
- In March 2018, the FDA expanded the indication for blinatumomab to pediatric and adult patients with B-ALL in first or second complete remission with MRD of $\geq 0.1\%$.

Clinical studies on blinatumomab in adults with refractory or relapsed B-ALL

- Blinatumomab was given to adults with Ph-positive ALL for which tyrosine kinase inhibitor (TKI)–based therapy was unsuccessful .
- During the first 2 cycles, complete remission with or without hematologic recovery was observed in 16 of 45 patients (36%), including 4 of 10 patients with the T315I mutation.

Clinical studies on blinatumomab in adults with refractory or relapsed B-ALL

- In another study, 9 adults with relapsed/refractory Ph-positive ALL and 3 patients with CML in blast crisis were treated with a combination of blinatumomab and a TKI (ponatinib [n = 8], dasatinib [n = 3], or bosutinib [n = 1]) . Three of 6 patients with overt hematologic disease and all 6 patients with MRD had complete remission with negative MRD response.

Clinical studies on blinatumomab in adults with refractory or relapsed B-ALL

- Due to its short half-life (approximately 2 hours), blinatumomab is administered as a continuous infusion . In one study, after an average of 2 days of infusion, B-cell counts dropped to less than $1/\text{mm}^3$ as a result of blinatumomab-induced apoptosis and they remained below the detection limit thereafter during infusion ..

Clinical studies on blinatumomab in adults with refractory or relapsed B-ALL

- The T cell counts declined within a day, recovered to baseline after 8–9 days, and expanded to more than twice the baseline count after 2–3 weeks of treatment, with an increase in the number of CD69-positive cells, consistent with polyclonal T cell activation.

Clinical studies on blinatumomab in adults with refractory or relapsed B-ALL

- During the first 2 days of infusion, transient release of the cytokines, interleukin (IL)-6, IL-10, and interferon (INF)- γ was observed. Long-term survivors (MRD responders who survived for 30 months or longer) had greater expansion of T cells and effector memory T cells when compared with non-responders and those with shorter survival (<30 months), suggesting the importance of T-cell expansion

Pediatric experience with blinatumomab

- In a phase I/II study, the recommended blinatumomab dosage for pediatric patients with relapsed/refractory ALL with a high disease burden ($>25\%$ bone marrow blasts) was $5 \mu\text{g}/\text{m}^2/\text{day}$ for the first 7 days, followed by $15 \mu\text{g}/\text{m}^2/\text{day}$ thereafter .

Pediatric experience with blinatumomab

- Complete remission within the first 2 cycles was seen in 27 of 70 patients (39%) who were treated at the recommended dose, with 14 of these responders (52%) having negative MRD.

Pediatric experience with blinatumomab

- In another phase III trial in pediatric patients with B-ALL at high risk of relapse, blinatumomab was compared with conventional consolidation therapy. The patient enrollment was terminated early because superior disease-free survival and overall survival, markedly lower toxicities, and better MRD clearance were observed in the blinatumomab arm .

Pediatric experience with blinatumomab

- Blinatumomab was given to pediatric patients with ALL in the setting of overwhelming chemotherapy-associated bacterial and fungal infections . This treatment resulted in the recovery of all patients and enabled successful bridging to further antileukemia therapy.

Pediatric experience with blinatumomab

- Blinatumomab was also effective and safe for eliminating MRD as a bridging therapy before HSCT in 15 other pediatric patients with B-ALL .

Adverse effects associated with blinatumomab treatment

- The unique and significant toxicities associated with blinatumomab are CRS and neurologic events . In the randomized phase III TOWER study, the incidences of neutropenia and infection (grade 3 and above) were lower for the blinatumomab arm than for the chemotherapy arm, but CRS was seen only in patients treated with blinatumomab .

Adverse effects associated with blinatumomab treatment

- The incidences of grade 3 or higher neurologic adverse effects were similar for both arms. In this study, patients who received blinatumomab also had better health-related quality of life when compared with those who received chemotherapy .

Adverse effects associated with blinatumomab treatment

- Symptoms of CRS include pyrexia, headache, nausea, fatigue, and hypotension. CRS typically occurs within the first 2 days after the initiation of blinatumomab infusion, which coincides with the recovery and expansion of T cells and proinflammatory cytokine production .

Adverse effects associated with blinatumomab treatment

- The cytokines IL-6, IL-10, and INF- γ are also elevated in patients with hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS). Severe CRS is associated with higher leukemia burden and higher initial starting dose of blinatumomab and can lead to secondary HLH/MAS .

Adverse effects associated with blinatumomab treatment

- To prevent CRS, pre-phase dexamethasone and stepwise increases in blinatumomab dosing should be used for patients with morphologically evident overt disease. As IL-6 is primarily responsible for an inflammatory response, IL-6 receptor blockade by tocilizumab is effective at ameliorating blinatumomab-induced CRS .

Adverse effects associated with blinatumomab treatment

- Neurologic toxicities of any grade have been reported in 50% of patients, with a median onset of 7 days; these toxicities include headache, malaise, confusion, somnolence, disorientation, encephalopathy, and convulsions.

Adverse effects associated with blinatumomab treatment

- A possible mechanism for these neurologic effects is cytokine release after the disruption of the blood–brain barrier by activated T cells . Grade 3 or higher neurologic toxicities have occurred in approximately 15% of patients, and drug discontinuation and administration of dexamethasone are recommended for patients who experience such toxicities .

Adverse effects associated with blinatumomab treatment

- In the low-MRD setting, CRS was infrequent, and most of the neurologic adverse events could be reversed by interrupting the infusion and providing supportive care .

Adverse effects associated with blinatumomab treatment

- Hypogammaglobulinemia develops as a result of B-cell aplasia after blinatumomab treatment; therefore, monitoring of immunoglobulin G (IgG) levels is recommended, along with treatment with intravenous immunoglobulins as necessary .

Adverse effects associated with blinatumomab treatment

- Grade 3 or lower graft-versus-host disease has been reported in patients who received blinatumomab after HSCT, but no patients in that study required discontinuation of blinatumomab or hospitalization .

Mechanisms of resistance to blinatumomab treatment

- The loss of expression of CD19, the target of blinatumomab, is the major mechanism of resistance to blinatumomab treatment. This is described further in the section on CAR T-cells.

Mechanisms of resistance to blinatumomab treatment

- Blinatumomab can activate regulatory T cells, which leads to IL-10 production, suppresses effector T-cell proliferation, and reduces the cytotoxic activity of CD8 T cells against B-ALL cells .

Mechanisms of resistance to blinatumomab treatment

- A higher percentage of regulatory T cells in peripheral blood was associated with a lower rate of response to blinatumomab. Treatment with cyclophosphamide and/or fludarabine can reduce regulatory T cells . Furthermore, the use of checkpoint inhibitors, as in PD-1 blockade, may enhance the efficacy of blinatumomab by eliminating inhibitor signals.

Inotuzumab Ozogamicin

Mechanisms of action

- CD22 is expressed on more than 90% of B-ALL cells and mature B lymphocytes, but not on normal hematopoietic B-cell precursors, non-B lymphoid cells, myeloid cells, hematopoietic stem cells, or non-hematopoietic lineage cells . Therefore, CD22 is another attractive target for immunotherapy.

Inotuzumab Ozogamicin

Mechanisms of action

- Inotuzumab ozogamicin is a humanized CD22 monoclonal antibody conjugated to calicheamicin . After inotuzumab binds to CD22, the complex is rapidly internalized to lysosomal vesicles. Similar to the treatment with gemtuzumab ozogamycin , which targets CD33-positive myeloid cells, the acidic pH environment in the lysosome liberates calicheamicin.

Inotuzumab Ozogamicin

Mechanisms of action

- As a potent cytotoxic antitumor antibiotic, calicheamicin binds to DNA in the minor groove and causes double-strand DNA breaks and apoptotic cell death.

Clinical studies on inotuzumab in adults and children with refractory or relapsed B-ALL

- In phase I/II studies of inotuzumab at doses of 1.2 mg/m² to 1.8 mg/m² per cycle (over 3 to 4 weeks) for adults with CD22-positive refractory or relapsed ALL, the overall response rate was 57% to 68%, and 63% to 84% of the responders were MRD negative.

Clinical studies on inotuzumab in adults and children with refractory or relapsed B-ALL

- In a randomized phase III study in adults with relapsed ALL (the INO-VATE study), the complete remission rate was significantly higher in patients who received inotuzumab (80.7%) than in those who were treated with standard intensive chemotherapy (29.4%) ($P < 0.001$), with a higher MRD-negative rate among patients who experienced remission (78.4% vs. 28.1%, $P < 0.001$).

Clinical studies on inotuzumab in adults and children with refractory or relapsed B-ALL

- Inotuzumab treatment resulted in significantly longer remission (4.6 months vs. 3.1 months, $P = 0.03$), progression-free survival (5.0 months vs. 1.8 months, $P < 0.001$), and overall survival (7.7 months vs. 6.7 months, $P = 0.04$) than did standard intensive chemotherapy.

Clinical studies on inotuzumab in adults and children with refractory or relapsed B-ALL

- Inotuzumab ozogamicin was administered weekly for a total dose of 1.8 mg/m^2 per cycle (0.8 mg/m^2 on day 1 and 0.5 mg/m^2 on days 8 and 15) and was reduced to 1.5 mg/m^2 (0.5 mg/m^2 weekly) once patients experienced remission. Inotuzumab was approved by FDA as monotherapy for refractory and relapsed ALL in 2017 .

Clinical studies on inotuzumab in adults and children with refractory or relapsed B-ALL

- Inotuzumab has been combined with low-intensity chemotherapy agents such as mini-hyperfractionated cyclophosphamide, vincristine, and dexamethasone, along with methotrexate and cytarabine (m-HCVD) .

Clinical studies on inotuzumab in adults and children with refractory or relapsed B-ALL

- In that study, one dose of inotuzumab was given in each cycle (1.3 mg/m² for cycle 1 and 1 mg/m² for cycles 2 to 4) and each cycle was administered every 4 weeks.

Clinical studies on inotuzumab in adults and children with refractory or relapsed B-ALL

- Of the 59 patients treated, 46 (78%) had a morphologic complete response, and negative MRD was seen in 82% of these 46 patients within 3 cycles. Compared with historical controls treated with inotuzumab alone, patients treated with inotuzumab and m-HCVD, after adjusting for patient characteristics, had a significantly better overall response rate (75% vs. 63%, $P = 0.02$) and 1-year overall survival rate (43% vs. 27%, $P = 0.02$).

Clinical studies on inotuzumab in adults and children with refractory or relapsed B-ALL

- A retrospective analysis of an inotuzumab compassionate use program for pediatric patients found that, among 51 children with heavily pretreated relapsed/refractory ALL, complete remission was seen in 67% of the patients, with negative MRD in 71% of these responders .

Adverse effects and resistance mechanisms associated with inotuzumab treatment

- In the phase 3 randomized INO-VATE study, patient-reported outcomes analysis showed that patients who received inotuzumab also reported better quality of life, better functioning, and better symptom scores than did those who received standard chemotherapy .

Adverse effects and resistance mechanisms associated with inotuzumab treatment

- Although the incidence of grade 3 or higher **thrombocytopenia** was significantly lower for the inotuzumab arm, **liver-associated adverse events** were more common in that arm (occurring in 83 of 164 patients [51%]) than in the standard therapy arm (where they occurred in 49 of 143 patients [34%]). **Sinusoidal obstruction syndrome** of any grade occurred in only 1 patient (<1%) in the standard therapy arm but in 22 patients

Adverse effects and resistance mechanisms associated with inotuzumab treatment

- A study with a nonbinding antibody–calicheamicin conjugate, which contains the same linker as gemtuzumab ozogamicin and inotuzumab ozogamicin, was performed in cynomolgus monkeys. Three days after the calicheamicin conjugate was administered, microscopic evaluation of the liver revealed midzonal degeneration, loss of sinusoidal endothelial cells, and marked platelet accumulation in the sinusoids, which coincided with acute thrombocytopenia.

Adverse effects and resistance mechanisms associated with inotuzumab treatment

- Furthermore, on day 63, liver histopathology showed variable endothelial recovery and progression to a combination of sinusoidal capillarization and sinusoidal dilation/hepatocellular atrophy; this is consistent with early signs of sinusoidal obstruction syndrome and supports the proposed mechanism of target-independent liver damage by calicheamicin.

Adverse effects and resistance mechanisms associated with inotuzumab treatment

- In gemtuzumab, fractionated use and a longer interval between gemtuzumab and HSCT were associated with lower incidences of sinusoidal obstruction syndrome. Similarly, a weekly divided inotuzumab schedule, rather than a single dose during a treatment cycle, was associated with lower incidences of sinusoidal obstruction syndrome, liver dysfunction, and fever/hypotension and had similar efficacy when compared with a single-dose schedule in each course, given every 3 to 4 weeks.

Adverse effects and resistance mechanisms associated with inotuzumab treatment

- Bone marrow response was associated with inotuzumab cumulative AUC levels and not with peak inotuzumab levels, and sinusoidal obstruction syndrome was possibly related to peak inotuzumab levels.

Adverse effects and resistance mechanisms associated with inotuzumab treatment

- In adults with relapsed or refractory ALL and older patients with newly diagnosed ALL, a lower dose of inotuzumab with a fractionated schedule in combination with m-HCVD has been used: a total of 0.9 mg/m² during cycle 1 (fractionated into 0.6 mg/m² on day 2 and 0.3 mg/m² on day 8 of cycle 1) and a total of 0.6 mg/m² during each of cycles 2, 3, and 4 (fractionated into 0.3 mg/m² on day 2 and 0.3 mg/m² on day 8 of the subsequent 3 cycles) .

Adverse effects and resistance mechanisms associated with inotuzumab treatment

- Furthermore, this regimen prolongs the interval between the last dose of inotuzumab and HSCT and augments the depth of remission by adding 4 cycles of blinatumomab after the 4 inotuzumab-based cycles. These strategies have contributed to lower incidences of sinusoidal obstruction syndrome and improved survival when compared with historical controls.

Adverse effects and resistance mechanisms associated with inotuzumab treatment

- One mechanism of resistance to inotuzumab, downregulation of CD22, has been reported in a few pediatric cases . The modulation of the targeted antigen on leukemia cells is similar to the antigen loss observed in CD19-directed therapies, although the molecular mechanism of CD22 antigen loss has not yet been well characterized.

Chimeric Antigen Receptor T cells

Mechanisms of action

- CD19 single-targeting CAR T-cell therapy has recently emerged as a new modality to treat B-lineage malignancies. A single-chain variant fragment (scFv) domain directed against a B-lineage–associated CD19 antigen activates intracellular signaling domains such as 4–1BB with CD3 ζ (19–BB ζ) or CD28 with CD3 ζ (19–28 ζ) .

Chimeric Antigen Receptor T cells

Mechanisms of action

- CAR gene-modified T-cell interaction with target cells occurs in a human leukocyte antigen (HLA)–independent fashion; therefore, a single vector can be used to treat all patients with cancers that express the target antigen.

Chimeric Antigen Receptor T cells

Mechanisms of action

- The B-cell marker CD19 is an excellent target in all B cell–derived malignancies because it is highly expressed on the surface of leukemia cells but is absent on cells of other lineages and on non-hemopoietic cells.

Chimeric Antigen Receptor T cells

Mechanisms of action

- Integrating signaling domains of the CD28 or 4–1BB costimulatory receptors in addition to the T-cell receptor ζ -chain domain in second-generation CARs improves their signaling properties and allows clonal expansion and persistence of CAR T cells *in vivo*.

Chimeric Antigen Receptor T cells

Mechanisms of action

- CAR T cells can be produced not only from autologous T cells but also from allogeneic T cells engrafted after a previous allogeneic HSCT at disease recurrence, which rarely cause graft-versus-host disease.

Clinical studies of CAR T cells in patients with refractory or relapsed B-ALL

- The first experience of using CAR T cells to treat B-ALL was reported in 2013. Two pediatric patients received 19-BBz CAR T cells, which expanded more than 1000 fold and were subsequently identified in bone marrow and cerebrospinal fluid for at least 6 months, with complete remission being observed in both patients .

Clinical studies of CAR T cells in patients with refractory or relapsed B-ALL

- Thereafter, a case series of 30 children and adults with B-ALL treated with 19-BBz CAR T cells at a single institution was reported; complete remission was observed in 27 of the patients (90%), even in those with blinatumomab-refractory disease or relapse after HSCT.

Clinical studies of CAR T cells in patients with refractory or relapsed B-ALL

- At 6 months, the disease-free survival was 67% and the overall survival was 78%. Three patients subsequently received an HSCT. The persistence of the CAR T cells and B-cell aplasia were important to maintaining remission.

- These efficacy and toxicity profiles were confirmed by a global collaborative study (ELIANA) of 75 pediatric and young adult patients. The overall remission rate was 81%, with all patients being negative for MRD. The event-free survival and overall survival were 73% and 90%, respectively, at 6 months and 50% and 76%, respectively, at 12 months.

- Most events were observed within 12 months after the CAR T-cell infusions. Persistence of CAR T cells was observed for up to 20 months. Only 8 patients in this study received a subsequent HSCT.

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- Patients treated with 19–28z CAR T cells have shown similar complete remission rates to patients treated with 19-BBz CART cells, with complete remission being observed in 67% of 21 pediatric and young adult patients in one study and in 83% of 53 adults in another study . However, compared with 19-BBz CAR T cells, more patients treated with 19–28z CAR T cells received a subsequent HSCT for long-term survival.

- The use of HSCT after CAR T-cell therapy is controversial, especially in patients who have not previously received an HSCT [62]. Most of the patients who received 19–28z CAR T cells and had remission in the early trials went on to HSCT . However, Park et al. reported no difference in event-free survival after remission with 19–28z CAR T-cell treatment between patients who received a subsequent HSCT and those who did not.

- Interestingly, CAR T cells migrate to extramedullary sites such as the central nervous system (CNS) or testes and, thus, can be used to treat isolated and combined extramedullary relapses .

Adverse effects associated with CAR T-cell treatment

The adverse effects of CAR T cells are on-target effects, which are usually reversible when the ALL cells have been eliminated or the engraftment/proliferation of the CAR T cells is complete .

Adverse effects associated with CAR T-cell treatment

Adverse effects associated with 19-BBz CAR T cells (tisagenlecleucel) included **CRS** (grade 3+4 [in 49% of patients]), **neurologic events** (grade 3 [in 18%]), febrile neutropenia (grade 3+4 [in 38%]), **prolonged cytopenias** (grade 3+4 [in 37%]), and **infections** (grade 3+4 [in 27%]) .

Adverse effects associated with CAR T-cell treatment

One patient died from each of the following conditions: cerebral hemorrhage in the context of coagulopathy and resolving cytokine release syndrome (15 days after infusion); HHV-6–positive encephalitis in association with prolonged neutropenia and lymphopenia; systemic mycosis in association with prolonged neutropenia; and unknown causes.

Adverse effects associated with CAR T-cell treatment

In CRS, which has also been reported in blinatumomab therapy, the pretreatment leukemia burden is associated with the severity of CRS because of the higher level of CAR T-cell expansion. The levels of cytokines such as IL-6 and IFN- γ are elevated, and an anti-IL-6 receptor antagonist, tocilizumab, has been approved by the FDA for treating CAR T-cell-induced CRS. Glucocorticoids are also considered when patients do not respond immediately to tocilizumab.

Adverse effects associated with CAR T-cell treatment

Predictive biomarker combinations for CRS have been reported and may guide clinicians in providing cytokine-directed therapy prophylactically or in the early phase of CRS . Early intervention for CRS with tocilizumab and/or corticosteroids reduced the incidence of transition from mild to severe CRS and had no detrimental effect on the MRD-negative complete remission rates or functional CAR T-cell persistence.

Adverse effects associated with CAR T-cell treatment

Neurotoxicity symptoms include encephalopathy, aphasia, delirium, tremor, and seizures; rare cases of rapid-onset and lethal diffuse cerebral edema have also been reported .

Adverse effects associated with CAR T-cell treatment

High pretreatment bone marrow disease burden, high CAR T-cell expansion, CRS, and pre-existing neurologic comorbidities were risk factors. Patients with severe neurotoxicity had signs of increased blood–brain barrier permeability.

Adverse effects associated with CAR T-cell treatment

Treatment is directed toward managing CRS and preventing seizures. As tocilizumab may not penetrate the CNS, an IL-6 antagonist may be considered. An updated CRS and neurologic toxicity grading scales have been published by the American Society for Transplantation and Cellular Therapy .

Adverse effects associated with CAR T-cell treatment

Infection after CAR T-cell therapy is more often seen during the first 28 days than at later time points, and the infections, which include invasive fungal infections, can be life threatening . Heavily pre-treated patient, higher CAR T-cell dose, and severe CRS were associated with an increased risk of infection.

Adverse effects associated with CAR T-cell treatment

The theoretical concerns regarding adverse reactions include an increased risk of secondary malignancy due to replication-competent retrovirus (RCR) or insertional mutagenesis. However, there have been no reports of RCR infection or insertional mutagenesis occurring. Because of the lentivirus transduction technology used to produce CAR T cells, some nucleic acid testing for human immunodeficiency virus type 1 can yield false-positive results .

Adverse effects associated with CAR T-cell treatment

Persistence of CAR T cells is associated with a late adverse reaction of prolonged hypogammaglobulinemia resulting from the off-tumor, on-target elimination of normal B cells . Patients experiencing this adverse event are treated with intravenous or subcutaneous immunoglobulins. However, several vaccine/pathogen-specific serum IgG and IgA titers remain relatively stable after CAR T-cell treatment because they are produced by memory B cell–independent long-lived CD19-negative plasma cells .

Mechanisms of resistance to CAR T-cell treatment

- One mechanism of resistance to CAR T-cell treatment is the loss of CAR T-cell persistence and B-cell aplasia. Early exhaustion of robust CAR T cells can limit their anti-leukemia activity; CD28 co-stimulation appears to augment the exhaustion induced by persistent CAR signaling, whereas 4-1 BB co-stimulation reduces it [77]. This may explain why 19-BBz CAR T cells are more persistent *in*

Cost analysis of CAR T-cell therapy

- The price of a single infusion of 19-BBz CAR T-cell therapy (tisagenlecleucel) is \$475,000, and it is planned to waive the charge for treatment that fails by 1 month after infusion. However, the actual cost of this therapy is estimated to be around \$1 million because of the costs of supportive care.

Cost analysis of CAR T-cell therapy

- Lin et al. estimated that tisagenlecleucel will be cost effective, when compared with currently available alternative treatments (bilantumomab, clofarabine/cyclophosphamide/etoposide combination, or clofarabine monotherapy),

Cost analysis of CAR T-cell therapy

- In a global study of 19-BBz CAR T-cell therapy, ELIANA, patient-reported quality of life was improved, according to all measured scores, at month 3 after infusion .

CAR T cells against T-ALL and allogeneic CAR T cells

- There have been several preclinical studies on the use of CAR T cells to treat T-cell malignancies. As targetable surface antigens are expressed on both normal and malignant T cells, CAR T-cell therapy can lead to fratricide of CAR T cells and immunodeficiency.

CAR T cells against T-ALL and allogeneic CAR T cells

- In one study, **anti-CD5** CAR T cells effectively eliminated CD5+ T-cell malignancies and caused fratricide mostly in the naïve T cells, whereas differentiated effector and memory T cells were selectively reserved . **CD1a** is expressed on cortical T-ALL cells and on developing cortical thymocytes, whereas neither CD34-positive progenitors nor extrathymic T cells express it .

CAR T cells against T-ALL and allogeneic CAR T cells

- Other studies found that downregulation of **CD7** by gene editing or the use of a protein expression blocker on anti-CD7 CAR T cells eliminated fratricide and that such CAR T cells were highly cytotoxic against CD7+ T-ALL cells. Interestingly, although these CAR T cells eliminated the primary T cells, they retained antiviral responses through their pre-existing naïve T-cell receptors.

Conclusions

- With the development of immunotherapy and molecular targeted therapy, as well as improved genomic sequencing, we are entering an exciting era of precision medicine. Replacing toxic chemotherapy with these novel therapies promises to improve not only the cure rate but also the quality of life for patients.

با تشکر از توجه شما

Survival of Children with Acute Lymphoblastic Leukemia

