(TKIs), such as imatinib, dasatinib, and nilotinib, constitute a part of the the main treatment for Ph+ ALL, which is characterized by the BCR-ABL1 fusion gene. Chemotherapy and/or steroids are frequently utilized in combination with TKIs. ABL001 provides a new method of ABL inhibition, although ponatinib works well against T315I mutations. Ph-like ALL: This type of ALL frequently contains CRLF2 rearrangements and ABL-class fusions, but it lacks the BCR-ABL1 fusion yet shares a comparable gene expression profile.(Jain & Abraham, 2020) For CRLF2-rearranged cases, JAK inhibitors like as ruxolitinib show promise, although conventional TKIs might work well for ABL-class fusions. KMT2A Rearranged ALL: KMT2A rearrangements are frequent in infant ALL and have an undesirable prognosis. (Richard-Carpentier vd., 2021)By targeting protein interactions and epigenetic changes, DOT1L and menin inhibitors,(Candoni & Coppola, 2024) such as SNDX-5613, are becoming potential therapeutic options. ETP ALL: A rare and aggressive type of T-cell ALL, ETP ALL can be identified by certain genetic changes and immunophenotypic markers.(Onishi vd., 2023) JAK inhibitors and Venetoclax, a BCL-2 inhibitor, are being studied as potential therapies for the dysregulated IL-7 and BCL-2 receptor pathways. Infant ALL: Challenges with infant ALL include an underdeveloped immune system and high frequency of KMT2A rearrangements. To improve those results, epigenetic modifiers and improved immunotherapeutic strategies, such as CAR T-cell therapy, are being researched. To sum it up, understanding the particular characteristics each high-risk ALL subtype is critical to designing personalised treatments. To overcome the difficulties presented by drug resistance and immune system infancy, ongoing research and clinical trials are important.

https://doi.org/10.1016/j.htct.2024.11.100

19

IMMUNOTHERAPY IN ALL: MONOCLONAL ANTIBODIES AND BEYOND

Fatma Arıkan

Marmara University, Pendik Educational and Research Hospital

In acute lymphoblastic leukemia (ALL) patients, overall survival is around 90% in childhood, whereas 5-year overall survival (OS) is less than 45% in adults. For eligible patients, allo-HCT remains the standard treatment, while immunotherapies are drawing attention in studies aimed at developing alternative treatment regimens. The most popular immunotherapies include bispecific antibodies (BsAbs), antibody-drug conjugates, CAR T-cell, and CAR NK cell therapies, which aim to target cancer cells using the patient's immune system. Blinatumomab is a bispecific T-cell-engaging (BiTE) antibody. It is designed to include binding regions that target two different antigens simultaneously. By binding to CD19 on B-ALL cells and CD3 on T cells, it activates T cells, leading to the polyclonal expansion of cytotoxic T cells, T cell activation, and the release of cytokines and cytotoxic granules, which cause the lysis of CD19+ lymphoblasts. Initially approved by the FDA in 2014 for the treatment of Ph(-) relapsed/refractory B-ALL, it has since received FDA approval for consolidation therapy in patients with MRD-positive disease as well as for MRD-independent consolidation therapy. Hematologic side effects are similar to those of standard chemotherapy, while non-hematologic side effects include cytokine release syndrome and neurological events, which are relatively manageable due to prophylactic measures and its short half-life. In the Alcantara study, it was shown that sustainable responses were achieved in patients with Ph(+) R/R ALL, despite the low number of patients enrolled in the study. Inotuzumab is an antibody-drug conjugate that consists of calicheamicin, a DNA-binding cytotoxic antibiotic, covalently linked to an anti-CD22 IgG4 mAb. In 2017, it received FDA approval after monotherapy with inotuzumab showed superiority over standard chemotherapy for relapsed/refractory CD22(+) B-ALL. The most common grade ≥3 side effects are hematologic and liver-related, including 11% VOD, which is mostly seen after sequential allo-HSCT. It is recommended for patients without known liver disease. To reduce VOD risk, it is advised to administer only up to two cycles of inotuzumab before SCT and avoid double alkylators in conditioning regimens. Inotuzumab monotherapy has shown high CR and MRD negativity rates when combined with low-intensity chemotherapy in elderly patients in first-line treatment, but it is still not approved by the FDA and EMA. Cell-based therapy, despite side effects limiting CAR T-cell, has shown remarkable efficacy in r/r B-ALL with CD19-targeted therapy, such as tisagenlecleucel (tisa-cel) for patients ≤25 years and brexucabtagene autoleucel for adults. Side effects include cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome (ICANS), and B-cell aplasia. For relapsed/refractory T-cell leukemia, CD5-CART, CD7-CART, and NS7CAR studies are ongoing. Although experimental, CAR-NK therapies using NK cells, which are isolated from peripheral blood and do not pose a GVHD risk, hold promise with fewer side effects, reduced relapse, and prolonged survival. Studies on immune checkpoint inhibitors in combination with other immunotherapies may be significant for B-ALL, while combinations of BCL-2 and BCL-XL inhibitors with chemotherapy may be important for T-ALL, which currently lacks antibody therapy. While challenges persist in treating T-ALL and Ph-like ALL, immunotherapy and cellular therapies continue to be significant for B-ALL treatment, with ongoing research into the optimal combinations and integration stages into therapy.

https://doi.org/10.1016/j.htct.2024.11.101

20

CAR-T CELL THERAPY IN ACUTE LEUKEMIAS

Serhat Çelik

Yıldırım Beyazıt University

Acute leukemias, particularly acute lymphoblastic leukemia (ALL) and, to a lesser extent, acute myeloid leukemia (AML), remain among the most challenging hematologic