(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

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## IMMUNOTHERAPY IN ALL: MONOCLONAL ANTIBODIES AND BEYOND

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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

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## CAR-T CELL THERAPY IN ACUTE LEUKEMIAS

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

malignancies due to high mortality rates and limited treatment options. In this context, Chimeric Antigen Receptor T (CAR-T) cell therapy has emerged as a promising approach for patients with refractory or relapsed disease. CAR-T cells are generated by genetically engineering the patient's T cells to express synthetic receptors targeting specific tumor-associated antigens. In ALL, CD19-targeted CAR-T cell therapies have demonstrated complete remission (CR) rates of 70–90%. For AML, ongoing research is exploring alternative targets. Clinical Studies and Outcomes ELIANA Trial The ELIANA trial, the largest global multicenter study of CD19-targeted CAR-T therapy, focused on pediatric and young adult ALL patients Tisagenlecleucel was infused into 75 ALL patients and evaluated for efficacy. The overall remission rate at 3 months was 81%, and all patients who responded to treatment were found to be negative for minimal residual disease by flow cytometry. Event-free survival and overall survival rates were 73% and 90% at 6 months and 50% and 76% at 12 months, respectively. Median duration of remission was not achieved. Tisagenlecleucel persisted in the blood for up to 20 months. Grade 3 or 4 adverse events thought to be related to tisagenlecleucel occurred in 73% of patients. Cytokine release syndrome occurred in 77% of patients, 48% of whom received tocilizumab. Neurological events occurred in 40% of patients and were managed with supportive care, and no brain edema was reported. ZUMA-3 Trial The ZUMA-3 an international, multicentre, single-arm, open-label study evaluating the efficacy and safety of the autologous anti-CD19 CAR-T-cell therapy KTE-X19 in adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia. KTE-X19 was administered to 55 (77%) patients. At a median follow-up of 16.4 months (13.8-19.6), 39 patients (71%; 95% CI 57-82, p<0.0001) had CR or CRi and 31 (56%) achieved CR. Median duration of remission was 12.8 months (95% CI 8.7 - not estimable), median relapse-free survival was 11.6 months (2.7-15.5) and median overall survival was 18.2 months (15.9 - not estimable). Among responders, median overall survival was not reached and 38 (97%) patients had MRD negativity. Ten (18%) patients received allo-SCT consolidation after KTE-X19 infusion. The most common adverse events of grade 3 or higher were anemia (27 [49%] patients) and pyrexia (20 [36%] patients). 14 (25%) patients had grade 3 or higher infections. Two grade 5 KTE-X19-related events occurred (cerebral herniation and septic shock). Grade 3 or higher cytokine release syndrome occurred in 13 (24%) patients, and grade 3 or higher neurologic events occurred in 14 (25%) patients. AML Target Studies AML poses unique challenges due to its heterogeneous cell populations. Early-phase studies of CD33-targeted CAR-T cells have shown promising tumor burden reductions in specific patient cohorts. However, these studies are still in the clinical validation phase. Future Perspectives Next-generation CAR-T cell designs aim to enhance target specificity and minimize adverse effects, improving the therapy's safety and efficacy profile. Allogeneic CAR-T platforms and universal CAR-T cell technologies are also under development, potentially increasing accessibility for a broader range of patients. In conclusion, CAR-T cell therapy represents a transformative step in personalized treatment strategies for acute leukemias. Continued advancements in clinical trials and translational research will further unlock the potential of this innovative approach in hematology.

https://doi.org/10.1016/j.htct.2024.11.102

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## PRECISION MEDICINE IN MULTIPLE MYELOM

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Precision medicine, an approach tailored to individual patient characteristics and disease profiles, has become increasingly important in the treatment of multiple myeloma (MM). Conventional MM treatment often yields variable results because the biological and clinical course of MM is heterogeneous. One of the main strategies in precision medicine for MM is genetic profiling. Certain genetic mutations such as t(4;14), t (14;16) and del(17p) are associated with a higher risk of aggressive disease. In addition, copy number alterations involving the long arm of chromosome 1 (1q) predict worse survival. In addition to cytogenetics, differential gene expression profile (GEP) signatures are independent prognostic factors for both PFS and OS, thus providing an additional method to identify high risk. By identifying these markers early, clinicians can classify patients into risk categories and tailor treatment accordingly. High-risk patients may receive more intensive treatments, while standard-risk patients may benefit from less aggressive regimens that preserve quality of life. Targeted therapies are another critical component of precision medicine in MM. Unlike conventional chemotherapy, which affects both cancerous and healthy cells, targeted therapies are designed to act specifically on the molecular pathways that drive MM cell growth. Drugs such as proteasome inhibitors, immunomodulatory agents and monoclonal antibodies are designed to attack key mechanisms in MM cells. For example, proteasome inhibitors disrupt protein excretion pathways in cancer cells, leading to cell death, while monoclonal antibodies can mark MM cells for immune destruction. These therapies offer more effective and tolerable treatment options when matched to patients whose disease characteristics are compatible with the drug's mechanism. CAR-T cell therapy and bispecific antibodies are promising options for relapsed/refractory MM and offer significant disease reduction for patients with limited options. Precision medicine also plays a role in monitoring minimal residual disease (MRD), which refers to the small number of cancer cells that can remain after treatment and potentially cause relapse. Multiparameter flow cytometry (MFC) and next-generation sequencing (NGS) are the most common and standardised methods. Whole body MRI and PET/CT provide better assessment for extramedullary disease. Patients with MRD-negative status generally have better long-term outcomes, so precision medicine approaches can tailor treatment to MRD status, aiming for complete eradication of disease in patients with evidence of remaining cancer cells. Finally, clinical trials are essential to develop precision medicine in MM. Studies focused on biomarker-driven therapies and novel agents give