N-Acetyl- galactosamine, the ligand of the hepatic asialo-glycoprotein receptors, conjugated to a synthetic siRNA. It targets and degrades a region of the SERPINC1 gene mRNA, preventing antithrombin production and enhancing thrombin generation. Antithrombin is a potent anticoagulant which inactivates FIXa, activated factor X (FXa) and activated factor II (FIIa/thrombin). Therefore, fitusiran can correct the coagulation imbalance and prevent the bleeding phenotype. Concizumab is an IgG4 monoclonal antibody targeting tissue factor pathway inhibitor (TFPI). It presents an alternative therapy for HA and HB patients, both with and without inhibitors. TFPI is a coagulation inhibitor. It limits coagulation during the initiation of the coagulation cascade through inhibition of the tissue factor-activated factor VII (TF-FVIIa) complex and through FXa inhibition. Gene therapy presents a novel and effective treatment modality for hemophilia, potentially bypassing complications of other therapies. Gene therapy regimens consist of single infusions of a viral vector, which result in transduction of a gene coding for the deficient factor into patient hepatocytes. Current gene therapy regimens for hemophilia predominantly utilise adeno-associated virus (AAV) vectors to deliver the required gene. **Conclusion:** Current factor replacement poses numerous issues, resulting in poor adherence and reduced QoL. Inhibitor development presents a key limitation to factor replacement. EHL products, emicizumab, fitusiran, and concizumab (summarised in appear effective in patients with and without inhibitors, and their longer half-lives enable less frequent injections.

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OPTIMIZATION OF FIXED DURATION TREATMENT OPTIONS IN CHRONIC LYMPHOCYTIC LEUKEMIA: CURRENT DATA AND FUTURE DIRECTIONS

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Introduction of Bruton tyrosine kinase inhibitors (BTKi) and B-cell lymphoma 2 (Bcl-2) antagonists changed the historical approach to chronic lymphocytic leukemia (CLL). Fixed-duration, targeted combination of these novel agents have replaced chemoimmunotherapy and have become preferred treatment options. Benefit of treating asymptomatic early stage disease is yet to be shown and indications for treatment are still mostly guided by International Working Group for CLL (iwCLL) 2018 recommendations. However; risk stratification has also come to question as genetic studies such as 17p/TP53 mutations, IGHV mutation status showed better risk analysis following chemoimmunoterapy (CIT) era. BTKi and Bcl-2 inhibitors also led to investigations on duration of treatment (fixed duration versus continuous) and best combination that provides most overall survival (OS) and progression-free survival (PFS) benefit. Since most CLL patients are elderly, comorbidities limit treatment options and these comorbidities correlate with shorter OS. Prior studies have shown that young and fit patients benefited from first line CIT such as fludarabine, cyclophosphamide, rituximab (FCR) and FCR provided long term remissions in previously untreated patients. Advent of BTKi and venetoclax offered a better treatment option for older population with high Cumulative Illness Rating Scale (CIRS) with fewer side effects although negative impact of comorbidities persisted.[3] In recent years, trials such as CLL14 have included patients with CIRS>6 and low creatinine clearence and showed the FD obinituzumab plus venetoclax combination was superior and provided longer PFS compared with to obinituzumab plus chlorambucil (median, 76.2 vs 36.4 months; hazard ratio [HR], 0.40; 95% confidence interval [CI], 0.31-0.52; $P < .0001$). Treatment with FD ibrutinib plus venetoclax in older patients also provided better responses. PFS was significantly longer for ibrutinib-venetoclax compared to chlorambucil-obinutuzumab (hazard ratio, 0.216; 95% confidence interval [CI], 0.131 to 0.357; P<0.001). PFS remained higher including patients 65 years of age or older or with a CIRS >6.These studies have provided basis for the approval of FD ibrutinib plus venetoclax combinations and showed clear benefit compared with historical CIT. FD treatments versus continuous ibrutinib became the focus of recent trials as well as determination of optimal duration for any treatment. Although continuous ibrutinib is the treatment of choice, trials have shown increased PFS and OS with FD treatments. With ibrutinib and venetoclax combination 36 −month overall survival (OS) was >95% regardless of high-risk features. Following recent trials, minimal residual disease (MRD) status as well as its incorporation into treatment duration emerged as a marker to guide CLL treatment. Subgroup analysis of trials have reported better PFS in patients with MRD negativity. Recently MRD guided treatment was shown to be effective and re-initiation of treatment with ibrutinib plus venetoclax was able to achive MRD negativity following discontinuation of treatment. Trials with ibrutinib and next generation BTKi and venetoclax are expected to incorporate MRD to further expand its role as an independent risk factor for long term survival. MRD tailored treatments in clinical practice may allow for discontinuation of treatment and also predict relapse. Appropriate method to determine MRD status requires further data from trials.

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OPTIMISATION OF THERAPEUTIC APPROACHES FOR HIGH-RISK ALL SUBTYPES

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There are actually several subtypes of acute lymphoblastic leukemia (ALL), some of which are especially difficult to manage. The high risk ALL subtypes included in this overview are neonatal ALL, KMT2A rearrangement, Philadelphia chromosome-positive (Ph+), Philadelphia-like (Ph-like), and Early T-cell precursor (ETP). Ph+ ALL: Tyrosine kinase inhibitors

(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.

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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.

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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