AML and that suppression of HIF-1α induces apoptosis (4-5). It has also been shown that hypoxic environment and HIF pathway play an important role in the long-term survival of leukemic stem cells in the bone marrow. However, there are also studies showing that HIF-1α deficiency causes AML to progress more rapidly (6).Therefore, these findings indicate that the role of HIF-1α should be considered carefully in practical applications depending on specific conditions. Pre- and post-clinical studies targeting the HIF pathway are ongoing. The HIF pathway appears promising as a new therapeutic target.

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TARGETED THERAPIES IN AML: CURRENT AND FUTURE TRENDS

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Acute Myeloid Leukemia (AML) encompasses several subtypes defined by distinct cytogenetic and molecular characteristics, which complicates treatment and necessitates therapies that can target multiple pathways. Despite advancements, there remains a significant need for molecular treatments that can achieve long-term remissions and potentially cure this heterogeneous disease. In the past 5 to 6 years, the FDA has approved several targeted therapies for both newly diagnosed and relapsed/refractory AML. These novel therapeutics, along with others currently being investigated, have shown promising activity against AML and have improved outcomes for many patients. This presentation will explore various molecular mechanisms that contribute to the pathogenesis of AML and review current research into how these mechanisms are being targeted in treatment strategiesA **Approved Drugs:** Since the 1970s, the classical therapy for AML has consisted of cytarabine combined with an anthracycline (daunorubicin or idarubicin), famously known as the "7 + 3" regimen. The small-molecule FDA-approved drugs for AML over the last decade include IDH inhibitors (olutasidenib, ivosidenib, enasidenib), FLT3 inhibitors (gilteritinib, midostaurin), BCL-2 inhibitor (venetoclax), hypomethylating agents (azacitidine, decitabine), and CPX-351 (liposomal cytarabine and daunorubicin). **Non-Approved Drugs:** Several FLT3 inhibitors, such as sorafenib and quizartinib, have undergone clinical trials for acute myeloid leukemia (AML). However, the FDA did not approve these drugs due to various concerns regarding the trial data. Recent reports from 2021 highlighted an oxoindoline-based selective FLT3 inhibitor as a potential candidate for treating FLT3-ITD-positive AML, a condition associated with a poor prognosis. Additionally, a first-in-class hydrazide-based HDAC inhibitor was reported in 2022, and a promising CDK9 inhibitor for AML treatment was identified in 2021. Rearrangements of the KMT2A (MLL1) gene occur in up to 10% of acute leukemias. Moreover, the TP53 tumor suppressor gene is often inactivated in cancers due to loss-of-function mutations or missense mutations in the DNA-binding domain, occurring in nearly 50% of cases. Targeting mutant p53 to restore its function could provide a promising avenue for new therapeutics. APR-246 is a compound designed to reactivate mutant p53. **Conclusions:** While this presentation does not cover all targeted agents, many promising options are available. A continuous and dedicated focus on understanding the fundamentals of molecular genetics and epigenetics, along with ongoing monitoring of clonal evolution before and after treatment with these targeted therapies, could lead to innovative changes in treatment strategies. This may ultimately provide the most beneficial outcomes for patients of all ages.

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HEMOPHILIA: ADVANCES IN TREATMENTS

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Introduction: Hemophilia is an X-linked recessive disorder. It is divided into two different subtypes; hemophilia A (HA) and B (HB), which result from the deficiency or complete absence of clotting factors VIII (FVIII) and IX (FIX) respectively. Current management of HA and HB includes prophylactic factor replacement[1]. Neutralising antibodies, as inhibitors, can develop against the infused factor and that can complicate the management of hemophilia patients. If inhibitors develop, immune tolerance induction can potentially promote tolerance to exogenous FVIII or FIX, and bypassing agents (BPAs) such as recombinant factor VIIa (rFVIIa) and activated prothrombin complex concentrates (aPCC) can be used to circumvent factor use. Inhibitor development impacts negatively upon quality of life and treatment compliance, highlighting the need for improved therapies. Several novel pharmacological therapies developed for hemophilia aim to rebalance the clotting cascade. These therapies utilise a range of different mechanisms, namely: the extension of the circulating half-life of standard recombinant factors; the mimicking of factor VIII cofactor activity; rebalancing of coagulation through targeting of natural anticoagulants such as antithrombin and tissue factor pathway inhibitor; and inducing the production of endogenous factors with gene therapy. **Discussion:** Extended half−life products involves fusing FVIII or FIX to a protein with a long half-life. Albumin and the constant region (Fc) of IgG have long plasma half-lives as they bind to the neonatal Fc receptor, which is critical for the endogenous recycling of both IgG and albumin. Another method is PEGylation, where one or more PEG chains are covalently linked to rFVIII or rFIX. PEG chains interfere with the recombinant factors binding to their clearance receptors, thereby prolonging circulating half-life. Emicizumab, a recombinant humanised bispecific IgG antibody, mimics the cofactor function of the missing FVIII in HA. It simultaneously binds activated FIX (FIXa) and factor X (FX), bringing them into spatial proximity to promote FIXa-catalysed FX activation, thereby restoring haemostasis. Fitusiran, a novel therapy applicable to both HA and HB, consists of the amino acid,

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