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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15

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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16

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,