MRD will consistently provide clinical benefits or be sufficient to challenge established treatment strategies for CLL(Fisher et al.,2023; Wierda et al.,2021; Yang et al,2021). Complex karyotype (CK) in CLL is defined by at least three numerical or structural abnormalities in two or more metaphases within the same clone. CK is linked to advanced disease, unmutated IGHV, TP53 mutations, adverse FISH abnormalities, and telomere dysfunction. Even within the CK subgroup, heterogeneity exists in the number and type of aberrations. While CK is a significant prognostic marker, its predictive value and role in treatment remain uncertain. (Chatzikonstantinou et al., 2021). Advances in understanding epigenetics in CLL, including DNA methylation and microRNAs, may lead to targeted therapies(Zhang et al., 2024). In conclusion, CLL's genetic and epigenetic landscape is complex, with numerous chromosomal abnormalities and molecular mutations playing a critical role in disease progression, prognosis, and treatment outcomes. Ongoing studies into genetic biomarkers and MRD monitoring continue to refine our understanding of the disease, thereby providing the foundation for more individualized and potentially more effective treatment approaches in the future.

https://doi.org/10.1016/j.htct.2024.11.094

13

NEW GENERATION BTK INHIBITORS AND RESISTANCE IN CLL TREATMENT

Aysun Gönderen

Kütahya Health Sciences University

Chronic lymphocytic leukemia (CLL) is an indolent lymphoproliferative malignancy characterized by monoclonal B lymphocytosis. BCR signaling plays a critical role in B cell development and survival. Bruton Tyrosine Kinase inhibitors (BTKi) disrupt the BCR signaling pathway by inactivation of BTK, leading to inhibition of proliferation and survival of CLL cells. There are two classes of BTK inhibitors, covalent and non-covalent. İbrutinif is the first approved covalent BTKi (cBTKi) of its class. The second-generation cBTKi (acalabrutinib and zanubrutinib) were designed to increase selectivity against BTK and reduce off-target toxicity. Continuous therapy with BTKi contributes to the acquisition of secondary resistance leading to clinical relapse. Pirtobrutinib, a noncovalent BTKi (ncBTKi), represents a novel class of BTKi developed to improve effectiveness and overcome acquired resistance to cBTKi. Mutations in BTK, particularly in the c481s region, and mutations in the PLCG2 region are considered the predominant mechanism of BTKi resistance in patients with CLL. Pirtobrutinib, retains kinase inhibition even in the presence of a BTK C481 mutation and demonstrates high specificity for BTK, with minimal off-target effects. The toxicity profiles of BTKis are closely linked to their kinase-binding patterns, including both on-target inhibition of BTK and variable off-target inhibition of other kinases, such as interleukin-2-inducible T-cell kinase (ITK), tyrosine kinase expressed in hepatocellular carcinoma (TEC), and epidermal growth factor receptor (EGFR) family kinases. AEs such as cardiac arrhythmias, bleeding, diarrhea, arthralgia, hypertension and infection are the primary reasons for ibrutinib discontinuation. Optimal management of AEs is crucial to achieving good outcomes and maintaining quality of life.

https://doi.org/10.1016/j.htct.2024.11.095

14

THE HYPOXIA INDUCIBLE FACTOR (HIF) PATHWAY IN AML: THERAPEUTIC TARGETING

Büşra Tuğçe Akman

Şırnak State Hospital

The increase in levels of the hormone erythropoietin, which leads to increased production of red blood cells in response to hypoxia, was a physiological response known in the early 20th century. However, the mechanism of the cellular reaction to hypoxia was unknown. William G. Kaelin Jr., Peter J. Ratcliffe, and Gregg L. Semenza received the 2019 Nobel Prize in Physiology and Medicine for their contributions to this field. HIFs have been identified as transcription factors that function in response to hypoxia. When oxygen levels are low, the HIF protein complex is protected from degradation and accumulates in the nucleus, where it connects with the aryl hydrocarbon receptor nuclear translocator (ARNT/HIF1-β) and binds to specific DNA sequences (HREs) in hypoxia-regulated genes. At normal oxygen levels, HIF-1α is rapidly degraded by the proteasome. Oxygen regulates the degradation process by adding hydroxyl groups (OH) to HIF-1α. The VHL protein can then recognize HIF and form a complex that leads to its degradation in an oxygen-dependent manner (1,2). It is known that there are 3 types of HIF: HIF-1, HIF-2, and HIF-3. Hypoxia activates all three HIFs, with HIF-3 acting as a regulator by suppressing the gene expression of HIF-1 and HIF-2. All three HIFs consist of two subunits, α and β. The β subunit is consistently expressed in the nucleus, independent of oxygen levels, whereas the α subunit exhibits differential responses to hypoxia and normoxia, serving as the primary site for HIF-1 in tumorigenesis. To date, three isoforms of the HIF α-subunit have been identified; these are HIF-1α, -2α, and -3α. In particular, HIF-1α is the most extensively studied isoform and is generally expressed in human cells. HIF-2α is expressed only in specific tissues and cell types, such as the lung, kidney, and liver. HIF-3α is mainly expressed in heart, kidney, and lung epithelial cells. Two genes, ARNT1 and ARNT2, encode HIF-1β subunits. HIF1A, EPAS1, and HIF3A encode the HIF1/2/3α proteins, respectively. HIF-1a has been detected in high amounts in many types of cancer and is known to regulate the expression of over 100 genes.It has an effect on gene categories related to angiogenesis, energy metabolism, invasion and metastasis, proliferation and apoptosis-related proteins, immune evasion, and drug resistance, which are important steps in tumor homeostasis (3).This makes the HIF pathway a targetable focus in cancer treatment. Studies have shown that there is an increase in HIF-1α and HIF-2α expression in

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.

https://doi.org/10.1016/j.htct.2024.11.096

15

TARGETED THERAPIES IN AML: CURRENT AND FUTURE TRENDS

Burcu Altındağ Avcı

Tekirdağ City Hospital

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.

https://doi.org/10.1016/j.htct.2024.11.097

16

HEMOPHILIA: ADVANCES IN TREATMENTS

Nurgül Karakaya

Necip Fazıl City Hospital

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,