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.

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NEW GENERATION BTK INHIBITORS AND RESISTANCE IN CLL TREATMENT

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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.

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

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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